Chapter 875

Logrank Tests with Proportional Hazards (Rubinstein and Wu)

Introduction

This module allows the sample size and power of the logrank test to be analyzed under the assumption of proportional hazards with uniform accrual and simple (proportional) loss to follow up. It was developed by Rubinstein (1981) based on the maximum likelihood test under the exponential model. Wu and Xiong (2015) derived the same formulas using a Weibull model. It was validated for use with the logrank test by Wu (2018).

A simulation study recorded in Wu (2018) showed that this procedure has comparable accuracy to the sample size formulas of Freedman (1982) and Schoenfeld (1981, 1983) when group sample sizes are equal, but is more accurate than these other tests when group sample sizes are unequal.

The logrank test is one of the most popular tests for comparing two survival distributions. It is easy to apply and is usually more powerful than an analysis based simply on proportions. It compares the survival time distributions of two groups.

The power calculations used here assume proportional hazards and are based on the number of events. In order to estimate sample sizes, an additional assumption is made that the underlying group distributions obey the proportional hazards assumption.

Technical Details

We assume that a study is to be made comparing the survival (or healing) of a treatment group with a control group (or a second treatment group). The control group consists of patients that will receive the existing treatment. In cases where no existing treatment exists, the control group consists of patients that will receive a placebo. The treatment group (group 1) will receive the new treatment.

We assume that the critical event of interest is death and that two treatments have survival time distributions with instantaneous death (hazard) rates, λ_1 and λ_2. These hazard rates are a subject's probability of death in a short period of time given that they are alive just before that time.

Hazard Ratio

There are several ways to compare two hazard rates. One is the difference, $\lambda_1 - \lambda_2$. Another is the ratio, λ_1/λ_2, called the hazard ratio.

$$HR = \frac{\lambda_1}{\lambda_2}$$

Note that since HR is formed by dividing the hazard rate of the treatment group by that of the control group, a treatment that has a smaller hazard rate than the control will have a hazard ratio that is less than one.

The hazard ratio may be formulated in other ways. If the proportions surviving during the study are called *S1* and *S2* for the treatment and control groups, the hazard ratio is given by

$$HR = \frac{\log(S_1)}{\log(S_2)}$$

Furthermore, if the median survival times of the two groups are *M1* and *M2*, the hazard ratio is given by

$$HR = \frac{M_2}{M_1}$$

Logrank Test

We assume that the standard (non-weighted) logrank test will be used to analyze the data. However, Cox's proportional hazards regression is often used to do the actual analysis.

The logrank statistic *L* is defined as

$$L = \frac{\sum_{i=1}^{d}\left(X_i - \frac{N_{1i}}{N_{1i}+N_{2i}}\right)}{\left[\sum_{i=1}^{d}\frac{N_{1i}N_{2i}}{(N_{1i}+N_{2i})^2}\right]^{1/2}}$$

where X_i is an indicator for the treatment group, N_{2i} is the number at risk in the control group just before the i^{th} event (death), and N_{1i} is the number at risk in the treatment group just before the i^{th} event (death).

The two-sided statistical hypotheses that are investigated by the logrank test are

$$H_0: HR = 1 \text{ vs. } H_a: HR \neq 1$$

The power of the logrank test is given by Wu (2018) page 73 as follows

$$Power = |\log HR|\tilde{\sigma} - z_{1-\alpha/k}$$

where *k* is 1 for a one-sided hypothesis test or 2 for a two-sided test, α is the error rate defined as usual, the *z* is the usual point from the standard normal distribution, and

$$\tilde{\sigma} = \sqrt{(d_1^{-1} + d_2^{-1})^{-1}}$$

$$d_i = N_i p_i$$

Assuming the exponential survival-time model with uniform accrual, the probability of death for an individual in group *i* is

$$p_i = 1 - \frac{1}{\lambda_i t_a}\left\{\exp(-\lambda_i t_f) - \exp\left(-\lambda_i(t_a + t_f)\right)\right\}$$

Let *W* be the proportion of subjects that are lost to follow up. Strictly speaking, these are individuals for which no information about their survival time is known. The effective sample size is

$$N_i^{adj} = N_i(1 - W)$$

Note that this calculation is carried out so that the adjusted sample size remains an integer.

Example 1 – Finding Sample Size for Various Accrual Times

A clinical trial is being planned to compare the effectiveness in increasing survival time from a particular disease of a new treatment. The current treatment for this disease achieves 50% survival after two years. The researchers want to find the sample size needed to detect an increase in percent surviving to 70%.

Testing will be done at the 0.05 significance level on a two-sided test. It is assumed that the group sample sizes will be equal. The follow-up time will be two years. The researchers want to compare the necessary sample sizes for accrual times of one, two, and three years.

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**
Group Allocation	**Equal (N1 = N2)**
W (Proportion Lost During Follow-Up)	**0**
Hazard Rates Input Type	**S1, S2 (Proportions Surviving)**
S1 (Proportion Surviving - Group 1)	**0.7**
S2 (Proportion Surviving - Group 2)	**0.5**
T0 (Time of S1 and S2)	**2**
Ta (Accrual Time)	**1 2 3**
Tf (Follow-Up Time)	**2**

Output

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

Numeric Reports

Numeric Results (Sample Size)

Solve For:	Sample Size
Groups:	1 = Treatment, 2 = Control
Hypothesis Type:	Two-Sided
Test Statistic:	Logrank Test
Events Assumption:	Proportional Hazards
Sample Size Assumption:	Exponential Data
Accrual Type:	Uniform
T0 (Time of S1 and S2):	2

	Sample Size			Proportion Lost During Follow-Up	Time		Hazard Ratio	Hazard Rate		Proportion Surviving		
Power	N1	N2	N	W	Accrual Ta	Follow-Up Tf	HR	λ1	λ2	S1	S2	Alpha
0.90120	108	108	216	0	1	2	0.51457	0.17834	0.34657	0.7	0.5	0.05
0.90263	96	96	192	0	2	2	0.51457	0.17834	0.34657	0.7	0.5	0.05
0.90156	87	87	174	0	3	2	0.51457	0.17834	0.34657	0.7	0.5	0.05

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1, N2, and N	The sample size (number of subjects) in the treatment group, the control group, and their total, respectively. Note that these estimates assume that the data are exponentially distributed.
W	The proportion of subjects lost to follow-up during the study. These are subjects that drop out for non-treatment reasons such as moving.
Ta	The length of the accrual time during which subjects are added to the study.
Tf	The length of the follow-up time after the last subject is added to the study.
HR	The hazard ratio is group 1's hazard rate divided by group 2's hazard rate. HR = λ1 / λ2.
λ1	The hazard rate of group 1, the treatment group.
λ2	The hazard rate of group 2, the control group.
S1	The proportion surviving for at least a time of T0 in group 1.
S2	The proportion surviving for at least a time of T0 in group 2.
T0	The length of time on which S1 and S2 are based.
Alpha	The probability of rejecting a true null hypothesis.

Numeric Results (Events)

Solve For:	Sample Size
Groups:	1 = Treatment, 2 = Control
Hypothesis Type:	Two-Sided
Test Statistic:	Logrank Test
Events Assumption:	Proportional Hazards
Sample Size Assumption:	Exponential Data
Accrual Type:	Uniform
T0 (Time of S1 and S2):	2

	Number of Events			Proportion Lost During Follow-Up	Time		Hazard Ratio	Hazard Rate		Proportion Surviving		
Power	E1	E2	E	W	Accrual Ta	Follow-Up Tf	HR	λ1	λ2	S1	S2	Alpha
0.90120	39	62	101	0	1	2	0.51457	0.17834	0.34657	0.7	0.5	0.05
0.90263	39	61	101	0	2	2	0.51457	0.17834	0.34657	0.7	0.5	0.05
0.90156	40	60	100	0	3	2	0.51457	0.17834	0.34657	0.7	0.5	0.05

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
E1, E2, and E	The required number of events (failures) in the treatment group, the control group, and their total, respectively. E = E1 + E2. Note that these estimates are based on the proportional hazards assumption. That is, they do not require the data distribution to be exponential.
W	The proportion of subjects lost to follow-up during the study. These are subjects that drop out for non-treatment reasons such as moving.
Ta	The length of the accrual time during which subjects are added to the study.
Tf	The length of the follow-up time after the last subject is added to the study.
HR	The hazard ratio is group 1's hazard rate divided by group 2's hazard rate. HR = λ1 / λ2.
λ1	The hazard rate of group 1, the treatment group.
λ2	The hazard rate of group 2, the control group.
S1	The proportion surviving for at least a time of T0 in group 1.
S2	The proportion surviving for at least a time of T0 in group 2.
T0	The length of time on which S1 and S2 are based.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group design will be used to test whether the Group 1 (treatment) distribution of the time to event is different from the Group 2 (control) distribution. The comparison will be made using a two-sided logrank test with a Type I error rate (α) of 0.05. The power and sample size calculations, based on the work of Rubinstein (1981) as described in Wu (2018), use the estimated number of events, which requires only the proportional hazards assumption. It is also assumed that the time to event data are exponentially distributed. The proportion lost to follow-up will be 0. The accrual time will be 1 and the follow-up time (time after complete accrual) will be 2. To detect a proportion surviving of 0.7 (in a time period of 2) in Group 1 when the proportion surviving in Group 2 is 0.5, with 90% power, the number of needed subjects will be 108 in Group 1 and 108 in Group 2 (totaling 216 subjects). The required number of events are 39 in Group 1 and 62 in Group 2 (totaling 101 events).

References

Rubinstein, L.V., Gail, M.H., and Santner, T.J. 1981. 'Planning the duration of a comparative clinical trial with loss to follow-up', Journal of Chronic Diseases, Vol. 34, pages 469-479.

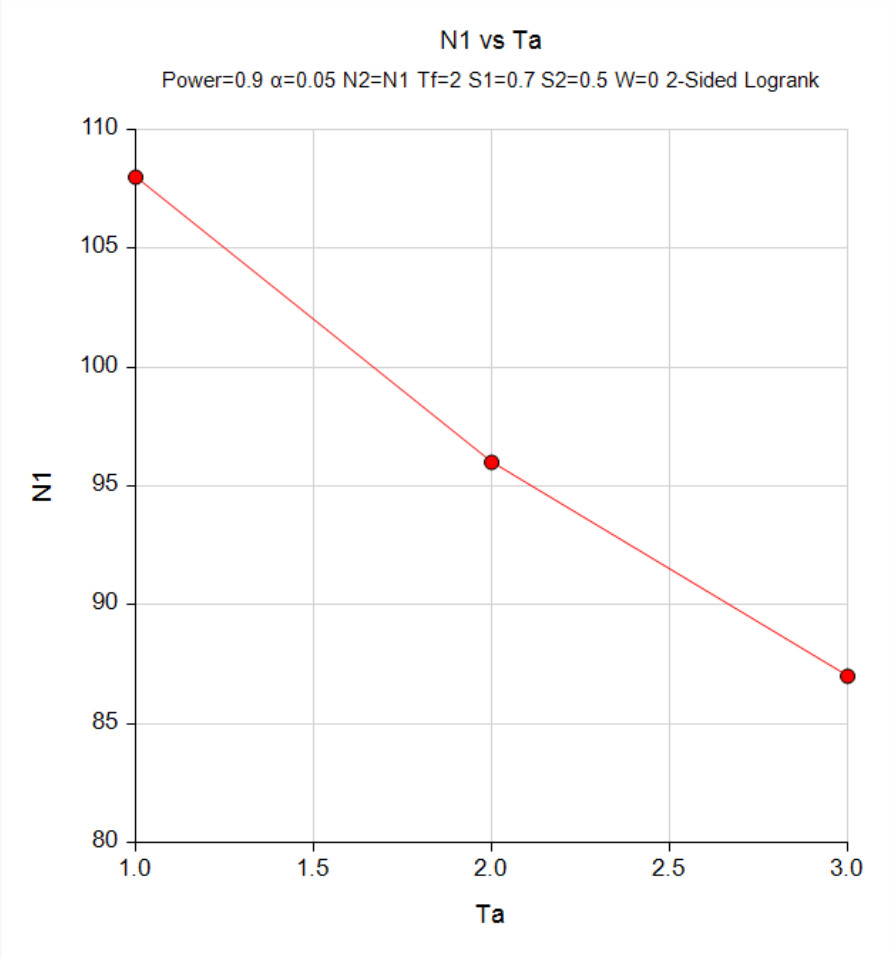
Wu, Jianrong. 2018. Statistical Methods for Survival Trial Design. CRC Press. Boca Raton.

Wu, J. and Xiong, X. 2015. 'Group sequential design for randomized phase III trials under the Weibull model', Journal of Biopharmaceutical Statistics, Vol. 25, pages 1190-1205.

This report shows the values of each of the parameters, one scenario per row. The sample size values from these tables are in the chart below.

Plots Section

Plots



This plot shows the relationship between sample size and accrual time.

Example 2 – Validation Using Wu (2018)

Wu (2018) page 73 presents an example in which a one-sided test with alpha = 0.05, power = 0.90, W = 0, Ta = 5, Tf = 3, S1 = 0.6, S2 = 0.5, and T0 = 3. He reports a total sample size of 571.

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	**0.90**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
W (Proportion Lost During Follow-Up)	**0**
Hazard Rates Input Type	**S1, S2 (Proportions Surviving)**
S1 (Proportion Surviving - Group 1)	**0.60**
S2 (Proportion Surviving - Group 2)	**0.50**
T0 (Time of S1 and S2)	**3**
Ta (Accrual Time)	**5**
Tf (Follow-Up Time)	**3**

Output

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

Numeric Reports

Numeric Results (Sample Size)

Solve For:	Sample Size
Groups:	1 = Treatment, 2 = Control
Hypothesis Type:	One-Sided
Test Statistic:	Logrank Test
Events Assumption:	Proportional Hazards
Sample Size Assumption:	Exponential Data
Accrual Type:	Uniform
T0 (Time of S1 and S2):	3

	Sample Size			Proportion Lost During Follow-Up	Time		Hazard Ratio	Hazard Rate		Proportion Surviving		
Power	N1	N2	N	W	Accrual Ta	Follow-Up Tf	HR	λ1	λ2	S1	S2	Alpha
0.90009	285	285	570	0	5	3	0.73697	0.17028	0.23105	0.6	0.5	0.05

Numeric Results (Events)

Solve For:	Sample Size
Groups:	1 = Treatment, 2 = Control
Hypothesis Type:	One-Sided
Test Statistic:	Logrank Test
Events Assumption:	Proportional Hazards
Sample Size Assumption:	Exponential Data
Accrual Type:	Uniform
T0 (Time of S1 and S2):	3

	Number of Events			Proportion Lost During Follow-Up	Time		Hazard Ratio	Hazard Rate		Proportion Surviving		
Power	E1	E2	E	W	Accrual Ta	Follow-Up Tf	HR	λ1	λ2	S1	S2	Alpha
0.90009	170	201	370	0	5	3	0.73697	0.17028	0.23105	0.6	0.5	0.05

PASS calculated the total sample size to be 570. The difference between this and Wu's result is due to rounding.