

Chapter 702

Logrank Tests (Freedman)

Introduction

This module allows the sample size and power of the logrank test to be analyzed under the assumption of proportional hazards. Time periods are not stated. Rather, it is assumed that enough time elapses to allow for a reasonable proportion of responses to occur. If you want to study the impact of accrual and follow-up time, you should use the one of the other logrank modules available in **PASS**. The formulas used in this module come from Machin *et al.* (2018). They are also given in Fayers and Machin (2016) where they are applied to sizing quality of life studies. They were originally published in Freedman (1982) and are often referred to by that name.

A clinical trial is often employed to test the equality of survival distributions for two treatment groups. For example, a researcher might wish to determine if Beta-Blocker A enhances the survival of newly diagnosed myocardial infarction patients over that of the standard Beta-Blocker B. The question being considered is whether the pattern of survival is different.

The two-sample t-test is not appropriate for two reasons. First, the data consist of the length of survival (time to failure), which is often highly skewed, so the usual normality assumption cannot be validated. Second, since the purpose of the treatment is to increase survival time, it is likely (and desirable) that some of the individuals in the study will survive longer than the planned duration of the study. The survival times of these individuals are then unobservable and are said to be *censored*. These times provide valuable information, but they are not the actual survival times. Hence, special methods have to be employed which use both regular and censored survival times.

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 survival across the whole spectrum of time, not at just one or two points.

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 exponential distribution. However, we are rarely in a position to assume exponential survival times in an actual clinical trial. How do we justify the exponential survival time assumption? First, the logrank test and the test derived using the exponential distribution have nearly the same power when the data are in fact exponentially distributed. Second, under the proportional hazards model (which is assumed by the logrank test), the survival distribution can be transformed to be exponential and the logrank test remains the same under monotonic transformations.

Comparison of Freedman Procedure to other PASS Logrank Procedures

The follow chart lists the capabilities and assumptions of several of the logrank procedures available in **PASS**.

Feature/Capability	Algorithm		
	Simple (Freedman)	Advanced (Lachin)	Markov Process (Lakatos)
Test Statistic	Logrank statistic	Mean hazard difference*	Logrank statistic
Hazard Ratio	Constant	Constant	Any pattern including time-dependent
Basic Time Distribution	Constant hazard ratio**	Constant hazard ratio (exponential)	Any distribution
Lost to Follow Up Parameters	Yes	Yes	Yes
Accrual Parameters	No	Yes	Yes
Drop In Parameters	No	No	Yes
Noncompliance Parameters	No	No	Yes
Duration Parameters	No	Yes	Yes
Input Hazard Ratios	No	No	Yes
Input Median Survival Times	No	No	Yes
Input Proportion Surviving	Yes	Yes	Yes
Input Mortality Rates	Yes	No	Yes

*Simulation shows power similar to logrank statistic

**Not necessarily exponential

Comparison of Results

It is informative to calculate sample sizes for various scenarios using several of the methods. The scenario used to compare the various methods was $S1 = 0.5$, $S2 = 0.7$, $T0 = 4$, Lost to Follow Up = 0.05, Accrual Time = 2, Total Time = 4, and $N = 200$. Note that the Freedman method does not allow the input of $T0$, Accrual Time, or Total Time, so it is much less comparable. The Lachin/Foulkes and Lakatos values are very similar.

Computation Method	S1	S2	T0	Lost to Follow Up	Accrual Time	Total Time	N	Power
PASS (Freedman)	0.5	0.7	?	0.05	0	?	200	0.7979
PASS (Lachin/Foulkes)	0.5	0.7	4	0.05	2	4	200	0.7219
PASS (Lakatos)	0.5	0.7	4	0.05	2	4	200	0.7144

Technical Details

We assume that a study is to be made comparing the survival (or healing) of a control group with an experimental group. The control group (group 1) consists of patients that will receive the existing treatment. In cases where no existing treatment exists, the group 1 consists of patients that will receive a placebo. The experimental group (group 2) will receive the new treatment.

We assume that the critical event of interest is death and that two treatments have survival 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.

Hazard Ratio

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

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

Note that since HR is formed by dividing the hazard rate of the experimental 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 S_1 and S_2 for the control and experimental groups, the hazard ratio is given by

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

Furthermore, if the median survival times of the two groups are M_1 and M_2 , the hazard ratio is given by

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

Logrank Test

We assume that the logrank test will be used to analyze the data once they are collected. However, often Cox's proportional hazards regression is used to do the actual analysis. The power calculations of the logrank test are based on several other parameters

$$z_{1-\beta} = \frac{|HR - 1| \sqrt{N(1-w)\varphi[(1-S_1) + \varphi(1-S_2)]/(1+\varphi)}}{(1+\varphi HR)} - z_{1-\alpha/k}$$

where k is 1 for a one-sided hypothesis test or 2 for a two-sided test, α and β are the error rates defined as usual, the z 's are the usual points from the standard normal distribution, w is the proportion that are lost to follow up, and φ represents the sample size ratio between the two groups.

$$\varphi = \frac{N_2}{N_1}$$

Note that the null hypothesis is that the hazard ratio is one, i.e., that

$$H_0: \frac{\lambda_2}{\lambda_1} = 1$$

Example 1 – Finding the Power

A clinical trial is being planned to test the effectiveness of a new treatment compared to the existing treatment. The current treatment for this disease achieves 50% survival after two years. The researchers want to compare various sample sizes when the proportion surviving in the experimental group is 0.7.

Testing will be done at the 0.05 significance level on a two-sided test. Per group sample size will range from 25 to 150. It is assumed that the group sample sizes will be equal.

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	Power
Null Hypothesis	Two-Sided
Alpha	0.05
Group Allocation	Equal (N1 = N2)
Sample Size Per Group	25 to 150 by 25
PL (Proportion Lost During Follow Up)	0
HR Input Type	Survival Proportions in Groups 1 and 2
S1 (Proportion Surviving in Group 1)	0.50
S2 (Proportion Surviving in Group 2)	0.70

Logrank Tests (Freedman)

Output

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

Numeric Reports

Numeric Results

Solve For: **Power**
 Groups: 1 = Control Group, 2 = Experimental
 Hypotheses: Two-Sided
 Distribution Assumption: Proportional Hazards

Power	Required Number of Events			Sample Size			Proportion Lost During Follow-Up PL	Proportion Surviving		Hazard Ratio HR	Alpha
	E1	E2	E	N1	N2	N		S1	S2		
0.29923	10	10	20	25	25	50	0	0.5	0.7	0.51457	0.05
0.52674	20	20	40	50	50	100	0	0.5	0.7	0.51457	0.05
0.69939	30	30	60	75	75	150	0	0.5	0.7	0.51457	0.05
0.81772	40	40	80	100	100	200	0	0.5	0.7	0.51457	0.05
0.89345	50	50	100	125	125	250	0	0.5	0.7	0.51457	0.05
0.93955	60	60	120	150	150	300	0	0.5	0.7	0.51457	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 E1 The required number of events in group 1.
 E2 The required number of events in group 2.
 E The total number of events required. $E = E1 + E2$.
 N1 The number of subjects in group 1, the control group.
 N2 The number of subjects in group 2, the experimental group.
 N The total sample size. $N = N1 + N2$.
 PL The anticipated proportion of subjects that will be lost during follow-up.
 S1 The proportion of group 1 subjects surviving to the end of the study without an event.
 S2 The proportion of group 2 subjects surviving to the end of the study without an event.
 HR The Hazard Ratio. $HR = \lambda_2 / \lambda_1$, where λ_1 and λ_2 are the hazard rates of groups 1 and 2, respectively. Note that $1/\lambda_i$ is the average time until an event for a subject in group i .
 Alpha The probability of rejecting a true null hypothesis.

Summary Statements

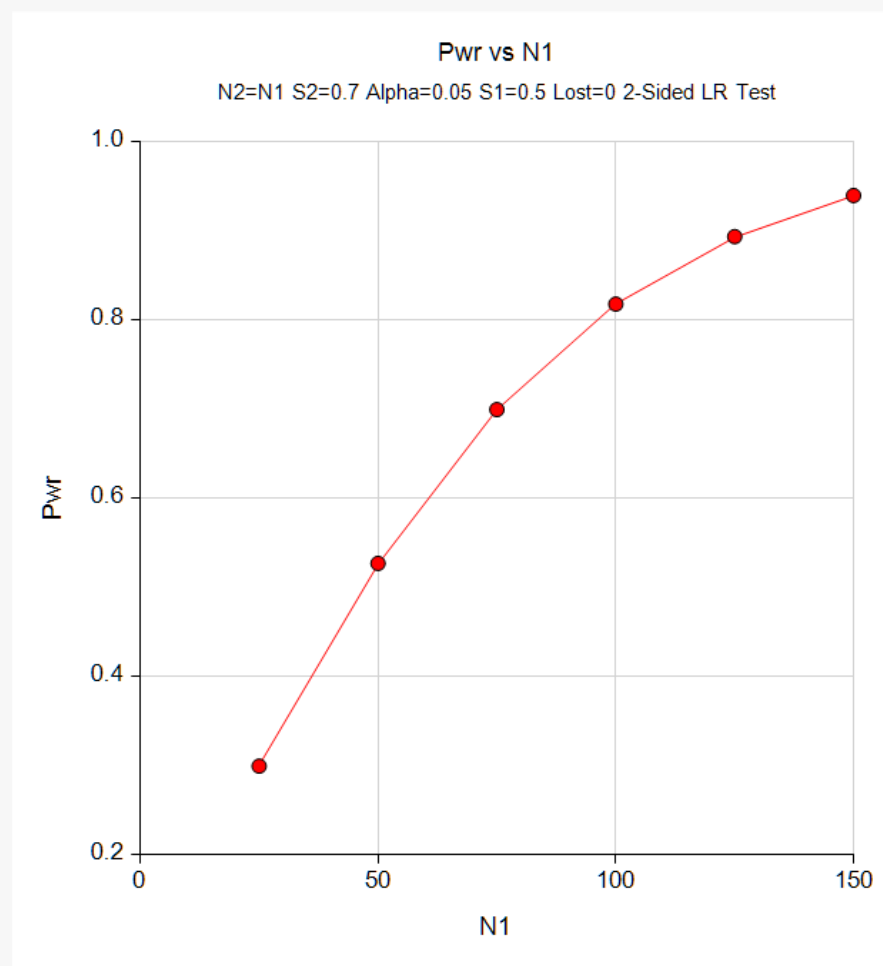
A parallel, two-group design will be used to test whether the Group 1 (control) proportion surviving is different from the Group 2 (experimental) proportion surviving (or, equivalently, whether there is a difference in hazard rate or event rate). The comparison will be made using a two-sided logrank test with a Type I error rate (α) of 0.05. It is anticipated that the proportion of subjects that are lost during follow-up is 0. To detect a hazard ratio (λ_2 / λ_1) of 0.51457, with a Group 1 proportion surviving of 0.5, and a Group 2 proportion surviving of 0.7, and with a sample size of 25 subjects in Group 1 and 25 subjects in Group 2 (totaling 50 subjects), the power is 0.29923. The corresponding number of events is 10 in Group 1 and 10 in Group 2 (totaling 20 events).

Logrank Tests (Freedman)

References

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- Freedman, L.S. 1982. 'Tables of the Number of Patients Required in Clinical Trials using the Logrank Test'.
Statistics in Medicine, Vol. 1, Pages 121-129.
- Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2018. Sample Size Tables for Clinical Studies, 4th Edition.
John Wiley & Sons. Hoboken, NJ.
- Julious, S. A. 2010. Sample Sizes for Clinical Trials. Chapman & Hall/CRC. Boca Raton, FL.
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This report shows the values of each of the parameters, one scenario per row. The values from this table are in the chart below.

Plots Section**Plots**

This plot shows the relationship between power and sample size in this example.

Example 2 – Finding the Sample Size

Continuing with our example, the researchers decide to find the required sample sizes for a range of powers between 0.70 and 0.95. The survival proportion of the control group is again set to 0.5. The treatment group survival proportions will be set to 0.60, 0.62, and 0.65. The sample

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
Null Hypothesis.....	Two-Sided
Power.....	0.7 to 0.95 by 0.05
Alpha.....	0.05
Group Allocation	Equal (N1 = N2)
PL (Proportion Lost During Follow Up)	0
HR Input Type.....	Survival Proportions in Groups 1 and 2
S1 (Proportion Surviving in Group 1)	0.50
S2 (Proportion Surviving in Group 2)	0.60 0.62 0.64

Logrank Tests (Freedman)

Output

Click the Calculate button to perform the calculations and generate a report and the following plot.

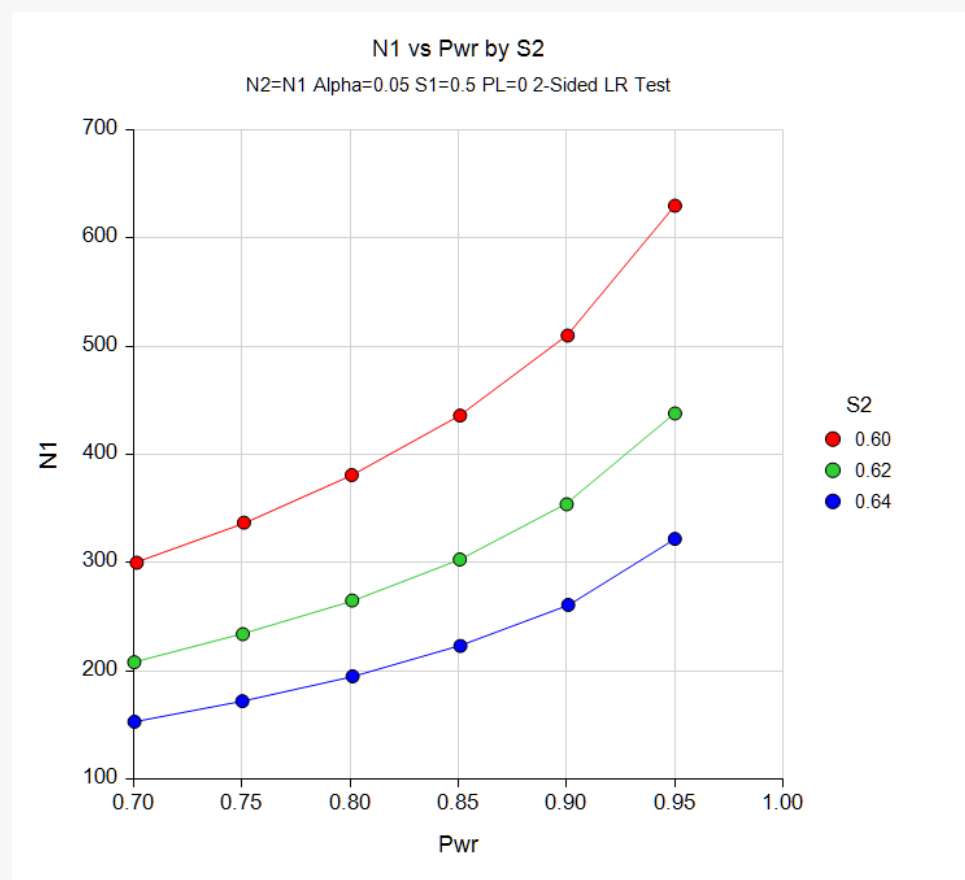
Numeric Results

Solve For: [Sample Size](#)
 Groups: 1 = Control Group, 2 = Experimental
 Hypotheses: Two-Sided
 Distribution Assumption: Proportional Hazards

Power	Required Number of Events			Sample Size			Proportion Lost During Follow-Up PL	Proportion Surviving		Hazard Ratio HR	Alpha
	E1	E2	E	N1	N2	N		S1	S2		
0.70137	135	135	270	300	300	600	0	0.5	0.60	0.73697	0.05
0.70019	92	92	184	208	208	416	0	0.5	0.62	0.68966	0.05
0.70028	66	66	132	153	153	306	0	0.5	0.64	0.64386	0.05
0.75090	152	152	304	337	337	674	0	0.5	0.60	0.73697	0.05
0.75038	103	103	206	234	234	468	0	0.5	0.62	0.68966	0.05
0.75016	74	74	148	172	172	344	0	0.5	0.64	0.64386	0.05
0.80072	172	171	343	381	381	762	0	0.5	0.60	0.73697	0.05
0.80090	117	117	234	265	265	530	0	0.5	0.62	0.68966	0.05
0.80113	84	84	168	195	195	390	0	0.5	0.64	0.64386	0.05
0.85078	197	196	393	436	436	872	0	0.5	0.60	0.73697	0.05
0.85065	134	133	267	303	303	606	0	0.5	0.62	0.68966	0.05
0.85091	96	96	192	223	223	446	0	0.5	0.64	0.64386	0.05
0.90050	230	229	459	510	510	1020	0	0.5	0.60	0.73697	0.05
0.90004	156	156	312	354	354	708	0	0.5	0.62	0.68966	0.05
0.90076	113	112	225	261	261	522	0	0.5	0.64	0.64386	0.05
0.95011	284	283	567	630	630	1260	0	0.5	0.60	0.73697	0.05
0.95011	193	193	386	438	438	876	0	0.5	0.62	0.68966	0.05
0.95005	139	138	277	322	322	644	0	0.5	0.64	0.64386	0.05

Logrank Tests (Freedman)

Plots



We will consider the chart since that allows us to understand the patterns more quickly. We note that changing S_2 from 0.60 (the top line) to 0.62 (the middle line) decreases the sample size requirements dramatically.

Example 3 – Validation using Machin (1997)

Machin *et al.* (1997) page 180 gives an example in which $S1$ is 0.25, $S2$ is 0.50, the one-sided significance level is 0.05, and the power is 90%. The per group sample size is 62. We will now run this example through **PASS**.

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 3** 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**
 Null Hypothesis **One-Sided**
 Power **0.9**
 Alpha **0.05**
 Group Allocation **Equal (N1 = N2)**
 PL (Proportion Lost During Follow Up) **0**
 HR Input Type **Survival Proportions in Groups 1 and 2**
 S1 (Proportion Surviving in Group 1) **0.25**
 S2 (Proportion Surviving in Group 2) **0.50**

Output

Click the Calculate button to perform the calculations and generate a report and the following plot.

Numeric Results

Solve For: [Sample Size](#)
 Groups: 1 = Control Group, 2 = Experimental
 Hypotheses: One-Sided
 Distribution Assumption: Proportional Hazards

Power	Required Number of Events			Sample Size			Proportion Lost During Follow-Up PL	Proportion Surviving		Hazard Ratio HR	Alpha
	E1	E2	E	N1	N2	N		S1	S2		
0.90141	39	39	78	62	62	124	0	0.25	0.5	0.5	0.05

PASS also calculated the per group sample size to be 62.

Example 4 – Validation based on a HADS Study using Fayers and Machin (2016)

Fayers and Machin (2016) give an example of the use of this procedure in conjunction with a Hospital Anxiety and Depression Scale (HADS) study. The HADS survey provides an ordinal score which has 22 categories. The HADS survey is administered soon after a subject is admitted into the trial. The subject is followed until they improve two steps on the HADS survey. The response is the number of days that were needed to achieve the two-category improvement (score decrease). This outcome is elapsed time and it can be analyzed with Kaplan-Meier curves and logrank tests such as those which are shown in this procedure.

The example on page 297 of Fayers and Machin (2016) is of a two-group study that compares the response to a new treatment (group 2) to that of the standard treatment (group 1). The hazard ratio that is to be detected is represented by two proportions of those that improved two-steps by the end of 12 weeks. These proportions are 0.65 in group 1 and 0.75 in group 2. The two-sided significance level is 0.05 and the required power is 80%. The estimated sample size is 660.

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 4** 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
Null Hypothesis	Two-Sided
Power.....	0.8
Alpha.....	0.05
Group Allocation	Equal (N1 = N2)
PL (Proportion Lost During Follow Up)	0
HR Input Type.....	Survival Proportions in Groups 1 and 2
S1 (Proportion Surviving in Group 1)	0.65
S2 (Proportion Surviving in Group 2)	0.75

Output

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

Numeric Results

Solve For: [Sample Size](#)
 Groups: 1 = Control Group, 2 = Experimental
 Hypotheses: Two-Sided
 Distribution Assumption: Proportional Hazards

Power	Required Number of Events			Sample Size			Proportion Lost During Follow-Up PL	Proportion Surviving		Hazard Ratio HR	Alpha
	E1	E2	E	N1	N2	N		S1	S2		
0.8003	99	99	198	330	330	660	0	0.65	0.75	0.66781	0.05

PASS calculated the total sample size to be 660. Note that 99 events per group are required. The sample size of 660 estimates how many subjects must be enrolled to achieve the required number of events.

Example 5 – Calculating Sample Size for a COVID-19 Clinical Trial

This example will show how this procedure might be used in planning a clinical trial to compare the effectiveness of a new treatment with the standard treatment in combatting COVID-19. The study outcome in each group will be the number of days it takes patients to advance two categories on a multi-point ordinal scale of disease status. The hypothetical trial being planned here will use the following six-point ordinal scale.

- 0) Discharge (alive).
- 1) Hospital admission, not requiring supplemental oxygen.
- 2) Hospital admission, requiring supplemental oxygen.
- 3) Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation.
- 4) Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation.
- 5) Death.

Each patient in the study is rated on this scale every day, and the response is the number of days until the disease status improves two categories. Suppose the hazard ratio that is to be detected by the study is the proportion is represented by the two proportions improving two-steps by the end of 14 days. These proportions are 0.40 in group 1 (control) and 0.55 in group 2 (treatment). The two-sided significance level is 0.05 and the required power is 0.80. The goal is to estimate the necessary sample size.

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 5** 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
Null Hypothesis	Two-Sided
Power	0.8
Alpha	0.05
Group Allocation	Equal (N1 = N2)
PL (Proportion Lost During Follow Up)	0
HR Input Type	Survival Proportions in Groups 1 and 2
S1 (Proportion Surviving in Group 1)	0.4
S2 (Proportion Surviving in Group 2)	0.55

Output

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

Numeric Results

Solve For: [Sample Size](#)
 Groups: 1 = Control Group, 2 = Experimental
 Hypotheses: Two-Sided
 Distribution Assumption: Proportional Hazards

Power	Required Number of Events			Sample Size			Proportion Lost During Follow-Up PL	Proportion Surviving		Hazard Ratio HR	Alpha
	E1	E2	E	N1	N2	N		S1	S2		
0.80003	89	89	178	169	169	338	0	0.4	0.55	0.65245	0.05

PASS calculated the total sample size to be 338. Note that 89 events per group are required.