

Chapter 699

Logrank Tests in a Cluster-Randomized Design

Introduction

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are put into the treatment group or the control group. In this case, the survival curves of two groups, made up of K_i clusters of M_{ij} individuals each, are to be tested using logrank test.

The formula used here is based on Xie and Waksman's (2003) extension of the results of Freedman (1982) that were quoted by Campbell and Walters (2014).

Technical Details

Our formulation comes from Campbell and Walters (2014). Denote an observation by Y_{ijk} where $i = 1, 2$ gives the group, $j = 1, 2, \dots, K_i$ gives the cluster within group i , and $k = 1, 2, \dots, m_{ij}$ denotes an individual in cluster j of group i . In this chapter, we will assume that group 1 is the control group and group 2 is the treatment group.

Let ρ denote the intracluster correlation coefficient (ICC) among individuals from the same cluster. This correlation is the correlation of censor indicator variable.

The formula for power is found by inverting the following sequence of formulas for sample size. Freedman (1982) showed that the number of events, e , needed for a power of $1 - \beta$ and a two-sided significance level of α to detect a hazard ratio of HR (h_2 / h_1) is given by

$$e = (z_{1-\alpha/2} + z_{1-\beta})^2 \frac{(1 + r HR)^2}{r(1 - HR)^2}$$

where $r = N_2 / N_1$ and $z_x = \Phi(x)$ is the standard normal distribution function. Note that for exponential survival, HR is related to S_1 and S_2 , the probabilities of survival (non-events) in the two groups, by

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

Logrank Tests in a Cluster-Randomized Design

Xie and Waksman (2003) showed that, in cluster trials, the above formula could be generalized to give the number of events needed in a cluster-randomized trial as follows.

$$e_c = e(1 + (\bar{M} - 1)\rho)$$

where \bar{M} is the average cluster size of all clusters given by

$$\bar{M} = \frac{K_1M_1 + K_2M_2}{K_1 + K_2}$$

The total number of subjects required is given by

$$N = N_1 + N_2 = (K_1 + K_2)\bar{M} = \frac{e_c(1 + r)}{1 - S_1 + r(1 - S_2)}$$

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.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *HR*, *S2*, *Power*, *K1*, and *M1*.

Under most situations, you will select either *Power* to calculate power or *K1* to calculate the number of clusters. Occasionally, you may want to fix the number of clusters and find the necessary cluster size.

Note that the value selected here always appears as the vertical axis on the charts.

The program is set up to calculate power directly. To find appropriate values of the other parameters, a binary search is made using an iterative procedure until an appropriate value is found.

Test

Ha (Alternative Hypothesis)

Specify whether the test is one-sided or two-sided. The one-sided option specifies a one-tailed test.

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.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is commonly used.

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

Logrank Tests in a Cluster-Randomized Design

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Values must be between zero and one. Usually, the value of 0.05 is used for alpha and this has become a standard. This means that about one test in twenty will falsely reject the null hypothesis. 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 – Number of Clusters & Cluster Size

Group 1 (Control)

K1 (Number of Clusters)

Enter a value (or range of values) for the number of clusters in the control group. You may enter a range of values such as *10 to 20 by 2*. The sample size for this group is equal to the number of clusters times the average cluster size.

M1 (Average Cluster Size)

This is the average number of subjects per cluster in group one. This value must be a positive number that is at least one. You can use a list of values such as *100 150 200*.

Group 2 (Treatment)

K2 (Number of Clusters)

This is the number of clusters in group two, the treatment group. This value must be a positive number. The sample size for this group is equal to the number of clusters times the number of subjects per cluster.

If you simply want a multiple of the value for group one, you would enter the multiple followed by *K1*, with no blanks. If you want to use *K1* directly, you do not have to premultiply by *1*. For example, all of the following are valid entries: *10 K1 2K1 0.5K1 K1*.

You can use a list of values such as *10 20 30* or *K1 2K1 3K1*.

M2 (Average Cluster Size)

This is the average number of subjects per cluster in group two. This value must be at least one.

If you simply want a multiple of the value for group one, you would enter the multiple followed by *M1*, with no blanks. If you want to use *M1* directly, you do not have to premultiply by *1*. For example, all of the following are valid entries: *10M1 2M1 0.5M1 M1*.

You can use a list of values such as *10 20 30* or *M1 2M1 3M1*.

Effect Size

S1 (Proportion Surviving - Control)

S1 is the proportion of subjects belonging to group 1 (controls) that are expected to survive during the study. Since *S1* is a proportion, it must be between zero and one. A value for *S1* must be determined either from a pilot study or from previous studies.

Use S2 or HR for Treatment Group

Specify whether the treatment group will be specified by entering S2 or HR.

Logrank Tests in a Cluster-Randomized Design

S2 (Proportion Surviving - Treatment)

S_2 is the proportion of patients belonging to group 2 (treatment) that are expected to survive during the study. Since S_2 is a proportion, it must be between zero and one.

This value is not necessarily the expected survival proportion under the treatment. Rather, it is the value that, if achieved, would be of special interest to clinicians.

HR (Hazard Ratio = h_2 / h_1)

Specify one or more hazard ratios. The null hypothesis is that the hazard ratio is one. The power is computed to detect this hazard ratio which is unequal to one.

An estimate of the hazard ratio may be obtained from the median survival times, from the hazard rates, or from the proportion surviving past a certain time point by pressing the *Survival Parameter Conversion Tool* button.

The range of HR is any positive number. Typical values of the hazard ratio are from 0.25 to 4.0.

ρ (Intracluster Correlation, ICC)

This is the value of the intracluster correlation coefficient. It may be interpreted as the correlation between any two censor indicator values in the same cluster.

Possible values are from 0 to just below 1. Typical values are between 0.0001 and 0.9.

You may enter a single value or a list of values.

Logrank Tests in a Cluster-Randomized Design

Example 1 – Calculating Power

Suppose that a cluster randomized study is to be conducted in which $S1 = 0.50$; $S2=0.6$; $\rho = 0.2$; $M1$ and $M2 = 4$ or 8 ; $\alpha = 0.05$; and $K1$ and $K2 = 5, 10, 15, 20,$ or 40 . Power is to be calculated for a two-sided test.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Logrank Tests in a Cluster-Randomized Design** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking on **Cluster-Randomized**, and then clicking on **Logrank Tests in a Cluster-Randomized Design**. 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>
Design Tab	
Solve For	Power
Alternative Hypothesis	Two-Sided
Alpha.....	0.05
K1 (Number of Clusters).....	5 10 15 20 40
M1 (Average Cluster Size)	4 8
K2 (Number of Clusters).....	K1
M2 (Average Cluster Size)	M1
S1 (Proportion Surviving – Control).....	0.50
Use S2 or HR for Treatment Group.....	S2
S2 (Proportion Surviving – Treatment)...	0.60
ρ (Intracluster Correlation, ICC).....	0.20

Annotated Output

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

Numeric Results

Numeric Results of Logrank Test													
Group 1 is the control group. Group 2 is the treatment group.													
	Subj Cnt	Subj Cnt	Evnt Cnt	Evnt Cnt	Clus Cnt	Clus Cnt	Clus Size	Clus Size	Haz Ratio	Prop Surv	Prop Surv	ICC	
	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	h2/h1	Gr 1	Gr 2	ρ	Alpha
Power	N1	N2	E1	E2	K1	K2	M1	M2	HR	S1	S2		
0.0732	20	20	9.0	9.0	5	5	4.0	4.0	0.7370	0.500	0.600	0.200	0.050
0.0848	40	40	18.0	18.0	5	5	8.0	8.0	0.7370	0.500	0.600	0.200	0.050
0.1072	40	40	18.0	18.0	10	10	4.0	4.0	0.7370	0.500	0.600	0.200	0.050
0.1291	80	80	36.0	36.0	10	10	8.0	8.0	0.7370	0.500	0.600	0.200	0.050
0.1400	60	60	27.0	27.0	15	15	4.0	4.0	0.7370	0.500	0.600	0.200	0.050
0.1726	120	120	54.0	54.0	15	15	8.0	8.0	0.7370	0.500	0.600	0.200	0.050
0.1726	80	80	36.0	36.0	20	20	4.0	4.0	0.7370	0.500	0.600	0.200	0.050
0.2157	160	160	72.0	72.0	20	20	8.0	8.0	0.7370	0.500	0.600	0.200	0.050
0.3004	160	160	72.0	72.0	40	40	4.0	4.0	0.7370	0.500	0.600	0.200	0.050
0.3817	320	320	144.0	144.0	40	40	8.0	8.0	0.7370	0.500	0.600	0.200	0.050

Logrank Tests in a Cluster-Randomized Design

References

- Campbell, M.J. and Walters, S.J. 2014. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Wiley. New York.
- Xie, T. and Waksman, J. 2003. 'Design and sample size estimation in clinical trials with clustered survival times as the primary endpoint.' Statist. Med. No. 22, pages 2835-2846.
- Jahn-Eimermacher, A., Ingel, K., and Schneider, A. 2013. 'Sample size in cluster-randomized trials with time to event as the primary endpoint.' Statist. Med. No. 32, pages 739-751.
- Gao, F., Earnest, A., Matchar, D.B., Campbell, M.J., and Machin, D. 2015. 'Sample size calculations for the design of cluster randomized trials: A summary of methodology.' Contemporary Clinical Trials, Volume 42, pages 41-50.

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

N_1 and N_2 are the number of subjects in groups 1 and 2, respectively. $N_1 = K_1 \times M_1$. $N_2 = K_2 \times M_2$.

E_1 and E_2 are the needed number of events in groups 1 and 2, respectively.

K_1 and K_2 are the number of clusters in groups 1 and 2, respectively.

M_1 and M_2 are the average number of subjects (items) per cluster in groups 1 and 2, respectively.

HR is hazard ratio, where $HR = (\text{treatment hazard}) / (\text{control hazard}) = \ln(S_2) / \ln(S_1)$.

S_1 is the proportion surviving (no events) in group 1, the control group.

S_2 is the proportion surviving (no events) in group 2, the treatment group.

ρ (ICC) is the intracluster correlation.

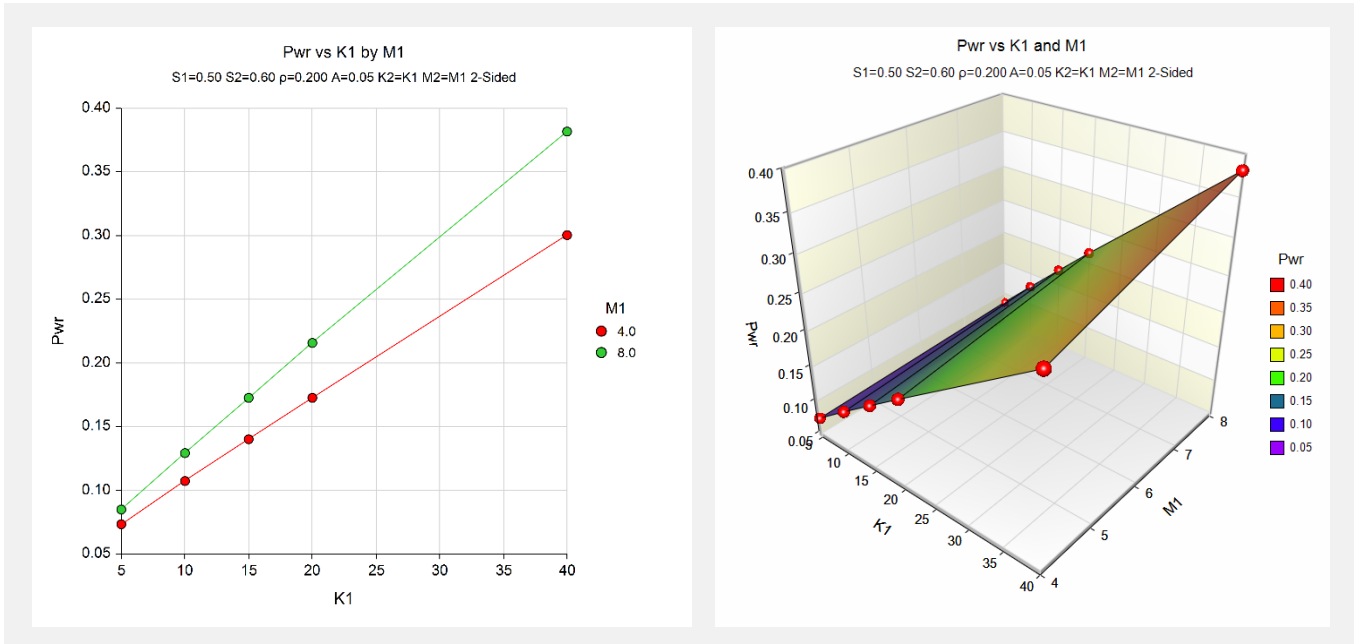
Alpha is the probability of rejecting a true null hypothesis, that is, rejecting when the means are actually equal.

Summary Statements

Sample sizes of 20 in group one (control) and 20 in group two (treatment), which were obtained by sampling 5 clusters with an average of 4.0 subjects per cluster in group one and 5 clusters with an average of 4.0 subjects per cluster in group two, achieve 7% power to detect a difference of at least 0.100 between the proportions surviving in group 1 (0.500) and in group 2 (0.600). This corresponds to detecting a hazard ratio of 0.7370. The intracluster correlation coefficient is 0.200. The power calculation assumes that a two-sided logrank test will be used with a significance level of 0.050. These results assume the hazard rates are proportional.

This report shows the power for each of the scenarios.

Plots Section



These plots show the power versus the cluster size for the two alpha values.

Logrank Tests in a Cluster-Randomized Design

Example 2 – Validation of Power Calculations using Xie and Waksman (2003)

Xie and Waksman (2003) on page 2840 presents a table of power values for various combinations of the parameters: $S1 = 0.223$; $S2 = 0.129$; $HR = 1.364$, $\rho = 0.0, 0.2, 0.4, 0.6, 0.8, 0.9$; $M1$ and $M2 = 2.7$; $\text{Alpha} = 0.05$; and Total Number of Clusters = 100, 200, 300, and 400. **PASS** can replicate the entire table, but we'll focus only on Total Number of Clusters = 200 (i.e. $K1 = K2 = 100$) for this example.

The reported power values for $\rho = 0.0$ to 0.9 with Total Number of Clusters = 200 are 0.90, 0.80, 0.71, 0.63, 0.56, 0.53, respectively.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Logrank Tests in a Cluster-Randomized Design** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking on **Cluster-Randomized**, and then clicking on **Logrank Tests in a Cluster-Randomized Design**. 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>
Design Tab	
Solve For	Power
Alternative Hypothesis	Two-Sided
Alpha.....	0.05
K1 (Number of Clusters).....	100
M1 (Average Cluster Size)	2.7
K2 (Number of Clusters).....	K1
M2 (Average Cluster Size)	M1
S1 (Proportion Surviving – Control).....	0.223
Use S2 or HR for Treatment Group.....	S2
S2 (Proportion Surviving – Treatment)...	0.129
ρ (Intracluster Correlation, ICC).....	0.0 0.2 0.4 0.6 0.8 0.9

Output

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

Numeric Results

Numeric Results of Logrank Test

Group 1 is the control group. Group 2 is the treatment group.

	Subj Cnt	Subj Cnt	Evnt Cnt	Evnt Cnt	Clus Cnt	Clus Cnt	Clus Size	Clus Size	Haz Ratio	Prop Surv	Prop Surv		
	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	h2/h1	Gr 1	Gr 2	ICC	Alpha
Power	N1	N2	E1	E2	K1	K2	M1	M2	HR	S1	S2	ρ	
0.9021	270	270	222.5	222.5	100	100	2.7	2.7	1.3648	0.223	0.129	0.000	0.050
0.8026	270	270	222.5	222.5	100	100	2.7	2.7	1.3648	0.223	0.129	0.200	0.050
0.7090	270	270	222.5	222.5	100	100	2.7	2.7	1.3648	0.223	0.129	0.400	0.050
0.6291	270	270	222.5	222.5	100	100	2.7	2.7	1.3648	0.223	0.129	0.600	0.050
0.5628	270	270	222.5	222.5	100	100	2.7	2.7	1.3648	0.223	0.129	0.800	0.050
0.5341	270	270	222.5	222.5	100	100	2.7	2.7	1.3648	0.223	0.129	0.900	0.050

PASS calculates the exact same power values.

Logrank Tests in a Cluster-Randomized Design

Example 3 – Validation of Sample Size Calculations using Gao et al. (2015)

Gao et al. (2015) on page 49 presents an example with $S1 = 0.75$; $S2 = 0.60$; $\rho = 0.05$ and 0.10 ; $M1$ and $M2 = 2$. To achieve 80% Power with Alpha = 0.05 with equal group sizes, they report a required group sample size of 164 and clusters per group of 82 for $\rho = 0.05$. They also report a required group sample size of 172 and clusters per group of 86 for $\rho = 0.10$.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Logrank Tests in a Cluster-Randomized Design** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking on **Cluster-Randomized**, and then clicking on **Logrank Tests in a Cluster-Randomized Design**. 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>
Design Tab	
Solve For	K1 (Number of Clusters)
Alternative Hypothesis	Two-Sided
Power	0.80
Alpha	0.05
M1 (Average Cluster Size)	2
K2 (Number of Clusters)	K1
M2 (Average Cluster Size)	M1
S1 (Proportion Surviving – Control)	0.75
Use S2 or HR for Treatment Group	S2
S2 (Proportion Surviving – Treatment) ...	0.60
ρ (Intracluster Correlation, ICC)	0.05 0.10

Output

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

Numeric Results

Numeric Results of Logrank Test													
Group 1 is the control group. Group 2 is the treatment group.													
	Subj Cnt	Subj Cnt	Evnt Cnt	Evnt Cnt	Clus Cnt	Clus Cnt	Clus Size	Clus Size	Haz Ratio	Prop Surv	Prop Surv	ICC	Alpha
	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	h2/h1	Gr 1	Gr 2	ρ	
Power	N1	N2	E1	E2	K1	K2	M1	M2	HR	S1	S2		
0.8039	164	164	53.3	53.3	82	82	2.0	2.0	1.7757	0.750	0.600	0.050	0.050
0.8044	172	172	55.9	55.9	86	86	2.0	2.0	1.7757	0.750	0.600	0.100	0.050

PASS matches their results exactly.