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, ..., K_i gives the cluster within group i, and k = 1, 2, ..., 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 – β and a two-sided significance level of α to detect a hazard ratio of HR (h_2 / h_1) is given by

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

where $r = N2 / N1$ 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

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

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

$$\bar{M} = \frac{K_1 M_1 + K_2 M_2}{K_1 + K_2}$$

The total number of subjects required is given by

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

Example 1 – Calculating Power

Suppose that a cluster randomized study is to be conducted in which *S1* = 0.50; *S2=0.6*; *ρ* = 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

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**
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 (Proportion Surviving - Treatment)**
S2 (Proportion Surviving - Treatment)	**0.60**
ρ (Intracluster Correlation, ICC)	**0.20**

Output

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

Numeric Reports

Numeric Results

Solve For: Power
Test Type: Logrank Test
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Two-Sided

	Number of Clusters			Cluster Size		Sample Size		Number of Events		Hazard Ratio	Proportion Surviving		ICC	
Power	K1	K2	K	M1	M2	N1	N2	E1	E2	HR	S1	S2	ρ	Alpha
0.0732	5	5	10	4	4	20	20	9	9	0.737	0.5	0.6	0.2	0.05
0.0848	5	5	10	8	8	40	40	18	18	0.737	0.5	0.6	0.2	0.05
0.1072	10	10	20	4	4	40	40	18	18	0.737	0.5	0.6	0.2	0.05
0.1291	10	10	20	8	8	80	80	36	36	0.737	0.5	0.6	0.2	0.05
0.1400	15	15	30	4	4	60	60	27	27	0.737	0.5	0.6	0.2	0.05
0.1726	15	15	30	8	8	120	120	54	54	0.737	0.5	0.6	0.2	0.05
0.1726	20	20	40	4	4	80	80	36	36	0.737	0.5	0.6	0.2	0.05
0.2157	20	20	40	8	8	160	160	72	72	0.737	0.5	0.6	0.2	0.05
0.3004	40	40	80	4	4	160	160	72	72	0.737	0.5	0.6	0.2	0.05
0.3817	40	40	80	8	8	320	320	144	144	0.737	0.5	0.6	0.2	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
K1, K2, and K The number of clusters in groups 1 and 2, and their total.
M1 and M2 The average number of items (subjects) per cluster in groups 1 and 2, respectively.
N1 and N2 The number of subjects in groups 1 and 2, respectively.
E1 and E2 The necessary number of events in groups 1 and 2, respectively.
HR The ratio of the hazards in group 2 and group 1. HR = haz2 / haz1.
S1 and S2 The proportions surviving (no events) in groups 1 and 2, respectively.
ρ The intracluster correlation (ICC). The correlation between a pair of subjects within a cluster.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group cluster-randomized design will be used to test whether the Group 1 (control) proportion surviving (S1) is different from the Group 2 (treatment) proportion surviving (S2) (or, equivalently, whether there is a difference in hazard rate). The comparison will be made using a two-sided logrank test with a Type I error rate (α) of 0.05. The hazard rates of the two groups are assumed to be proportional over time, and the intracluster correlation coefficient is assumed to be 0.2. To detect a proportion surviving difference of 0.1 (S1 = 0.5, S2 = 0.6), or, equally, a hazard ratio (h2 / h1) of 0.737, with 5 clusters of 4 subjects per cluster in Group 1 (totaling 20 subjects) and 5 clusters of 4 subjects per cluster in Group 2 (totaling 20 subjects), the power is 0.0732.

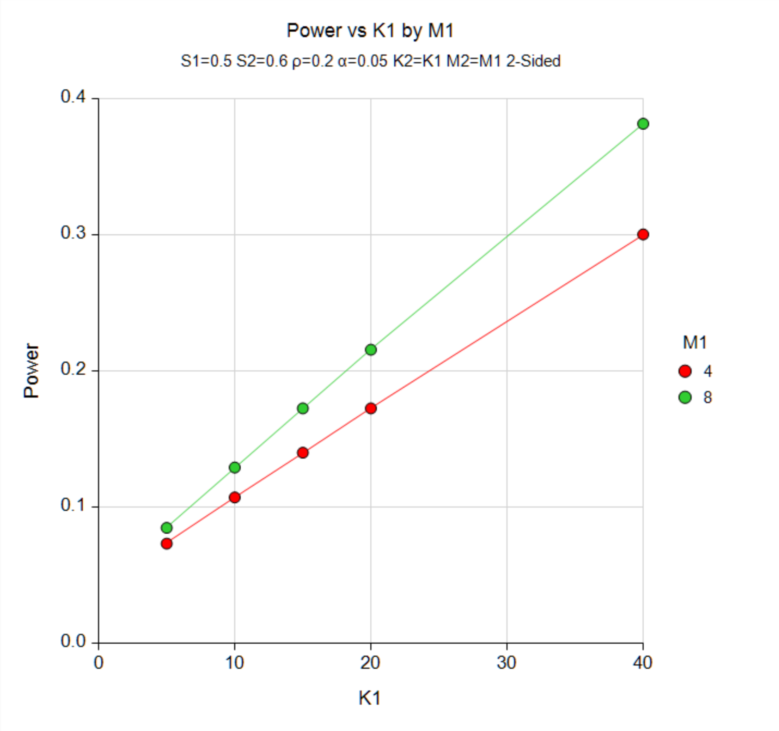
References

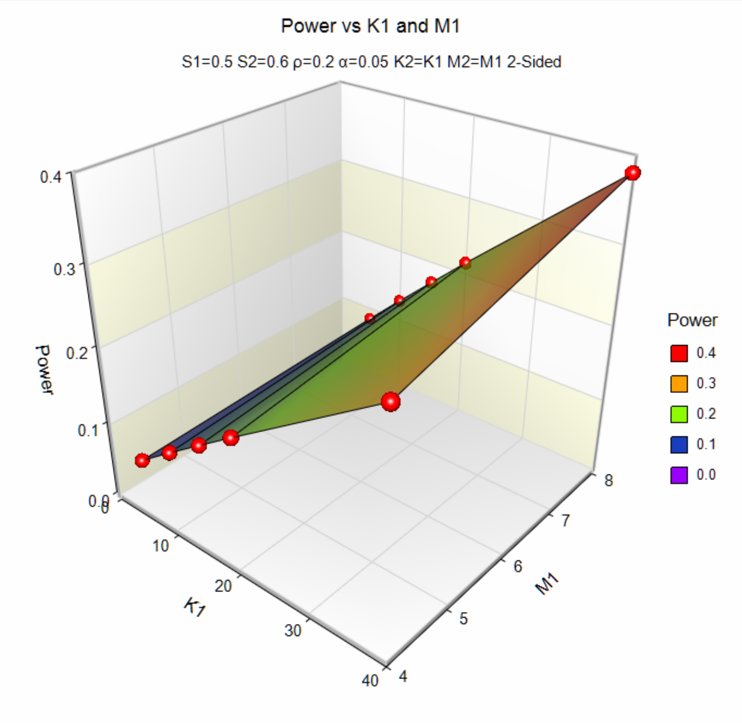
Campbell, M.J. and Walters, S.J. 2014. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Wiley. New York.
Gao, F., Earnest, A., Matchar, D.B., Campbell, M.J., and Machin, D. 2015. 'Sample size calculations for the design of cluster randomized trials: A summary of methodology.' Contemporary Clinical Trials, Volume 42, pages 41-50.
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.
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.

This report shows the power for each of the scenarios.

Plots Section

Plots





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

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, ρ = 0.0, 0.2, 0.4, 0.6, 0.8, 0.9; $M1$ and $M2$ = 2.7; 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 ρ = 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

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	**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 (Proportion Surviving - Treatment)**
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

Solve For: Power
Test Type: Logrank Test
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Two-Sided

	Number of Clusters			Cluster Size		Sample Size		Number of Events		Hazard Ratio	Proportion Surviving		ICC	
Power	K1	K2	K	M1	M2	N1	N2	E1	E2	HR	S1	S2	ρ	Alpha
0.9021	100	100	200	2.7	2.7	270	270	222.5	222.5	1.3648	0.223	0.129	0.0	0.05
0.8026	100	100	200	2.7	2.7	270	270	222.5	222.5	1.3648	0.223	0.129	0.2	0.05
0.7090	100	100	200	2.7	2.7	270	270	222.5	222.5	1.3648	0.223	0.129	0.4	0.05
0.6291	100	100	200	2.7	2.7	270	270	222.5	222.5	1.3648	0.223	0.129	0.6	0.05
0.5628	100	100	200	2.7	2.7	270	270	222.5	222.5	1.3648	0.223	0.129	0.8	0.05
0.5341	100	100	200	2.7	2.7	270	270	222.5	222.5	1.3648	0.223	0.129	0.9	0.05

PASS calculates the exact same power values.

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; ρ = 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 ρ = 0.05. They also report a required group sample size of 172 and clusters per group of 86 for ρ = 0.10.

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 .... **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 (Proportion Surviving - Treatment)**
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

Solve For: K1 (Number of Clusters)
Test Type: Logrank Test
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Two-Sided

	Number of Clusters			Cluster Size		Sample Size		Number of Events		Hazard Ratio	Proportion Surviving		ICC	
Power	K1	K2	K	M1	M2	N1	N2	E1	E2	HR	S1	S2	ρ	Alpha
0.8039	82	82	164	2	2	164	164	53.3	53.3	1.7757	0.75	0.6	0.05	0.05
0.8044	86	86	172	2	2	172	172	55.9	55.9	1.7757	0.75	0.6	0.10	0.05

PASS matches their results exactly.