Chapter 707

Tests for the Difference of Two Hazard Rates Assuming an Exponential Model

Introduction

A clinical trial is often employed to test the equality of survival distributions of two treatment groups. The two-sample t-test is not appropriate for two reasons. First, the data are not normally distributed. Second, some survival times are *censored*. For these reasons, special test statistics such as the logrank test have been developed. This module computes the sample size and power of the logrank test assuming survival times follow exponential distributions. Accrual time and follow-up time are included among the input parameters.

This procedure is based on the *unconditional* method of Chow, Shao, and Wang (2008) which, in turn, is based on the *conditional* methods of Lachin and Foulkes (1986). The conditional procedure does not extend to non-inferiority, non-zero null, or equivalence tests as easily as the unconditional method does (see Chow, Shao, and Wang (2008) page 173).

Technical Details

This section presents the *unconditional* method of Chow, Shao, and Wang (2008).

Basic Model

Suppose a clinical trial consists of two independent groups labeled “1” and “2” (where group 1 is the control group and group 2 is the treatment group). The total sample size is *N* and the sizes of the two groups are N_1 and N_2. Usually, you would plan to have $N_1 = N_2$.

Test Statistic

The power and sample size formulas presented below are for the logrank test statistic. However, they were originally developed for comparing the difference of two exponential hazard rates. Simulation studies then showed that they approximated the power of the logrank test.

Test Comparing Hazard Rate

The original test statistic is the difference of the hazard rates estimated by maximum likelihood divided by their standard error. The maximum likelihood estimate of an exponential hazard rate for a particular group is

$$\hat{h} = \frac{\text{number of events}}{\text{sum of study time of all subjects}}$$

Chow, Shao, and Wang (2008) indicate that the test statistic

$$Z = \frac{\hat{h}_2 - \hat{h}_1}{\sqrt{\frac{\sigma^2(\hat{h}_1)}{N_1} + \frac{\sigma^2(\hat{h}_2)}{N_2}}}$$

where

$$\sigma^2(h) = \frac{h^2}{1 + \frac{e^{-hT}(1 - e^{hR})}{hR}}$$

follows the standard normal standard normal distribution at least approximately.

Logrank Test

The logrank test statistic is given by

$$L = \frac{\sum_{k=1}^{K}\left(I_k - \frac{Y_{1i}}{Y_{1i} + Y_{2i}}\right)}{\left[\sum_{k=1}^{K}\left(\frac{Y_{1i}Y_{2i}}{(Y_{1i} + Y_{2i})^2}\right)\right]^{-1/2}}$$

Where K is the number of deaths, Y_{ij} is the number of subjects at risk just prior to the jth observed event in the ith group, and I_k is is a binary variable indicating whether the kth even is from group 1 or not. L follows the standard normal distribution.

Power Calculations

Assuming an exponential model with hazard rates h_1 and h_2 for the two groups, Chow et al. (2008) give the following equation relating *N* and power of a two-tailed test.

$$\frac{|h_2 - h_1|}{\sqrt{\frac{\sigma^2(h_1, \omega_1, A)}{N_1} + \frac{\sigma^2(h_2, \omega_2, A)}{N_2}}} - z_{1-\alpha/2} = z_{1-\beta}$$

where

$$\sigma^2(h_i, \omega_i, A) = \frac{h_i^2}{E(d_i|h_i, \omega_i, A)}$$

$$E(d_i|h_i, \omega_i, A) = \left(\frac{h_i}{h_i + \omega_i}\right)\left(1 + \frac{A\exp\{-(h_i + \omega_i)T\}[1 - \exp\{(h_i + \omega_i - A)R\}]}{(h_i + \omega_i - A)[1 - \exp\{-AR\}]}\right)$$

$$E(d_i|h_i, \omega_i, 0) = \left(\frac{h_i}{h_i + \omega_i}\right)\left(1 + \frac{\exp\{-(h_i + \omega_i)T\}[1 - \exp\{(h_i + \omega_i)R\}]}{(h_i + \omega_i)R}\right)$$

These parameters are interpreted as follows.

Parameter	**Interpretation**
$\sigma^2(h, \omega, A)$	Variance of $\hat{h}$
$E(d_i\|h_i, \omega_i, A)$	Expected proportion of events (deaths) in group *i*
d_i	Indicates a person does $(d_i = 1)$ or does not $(d_i = 0)$ die in group *i*
h_i	Hazard rate of group *i* (see below)
ω_i	Loss to follow-up hazard rate of group *i* (see below)
A	Patient entry parameter (see below)
R	Accrual time
T	Total time
$T - R$	Follow-up time

Exponential Distribution

The hazard rate from the exponential distribution, h, is usually estimated using maximum likelihood techniques. In the planning stages, you have to obtain an estimate of this parameter. To see how to accomplish this, let's briefly review the exponential distribution. The density function of the exponential is defined as

$$f(t) = h\exp\{-ht\}, \quad t \geq 0, h > 0.$$

The cumulative survival distribution function is

$$\mathrm{S}(t) = \exp\{-ht\}, \quad \mathrm{t} \geq 0.$$

Solving this for h yields

$$h = -\frac{\log\{S(t)\}}{t}$$

Note that $S(t)$ gives the probability of surviving t years. To obtain a planning estimate of h, you need only know the proportion surviving during a particular time period. You can then use the above equation to calculate h.

Patient Entry

Patients are enrolled during the accrual period. **PASS** lets you specify the pattern in which subjects are enrolled. Suppose patient entry times are distributed as $g(t)$ where t_i is the entry time of the i^{th} individual and $0 \leq t_i \leq R$. Let $g(t)$ follow the truncated exponential distribution with parameter A, which has the density

$$g(t) = \begin{cases} \dfrac{A\exp\{-At\}}{1 - A\exp\{-AR\}} & \text{if } 0 \leq t \leq R, \quad A \neq 0 \\ 1 & \text{otherwise} \end{cases}$$

where

R is accrual time.

A is interpreted as follows:

$A > 0$ results in a convex (faster than expected) entry distribution.

$A < 0$ results in a concave (slower than expected) entry distribution.

$A = 0$ results in the uniform entry distribution in which $g(t) = 1/R$.

Rather than specify A directly, **PASS** has you enter the percentage of the accrual time that will be needed to enroll 50% of the subjects. Using an iterative search, the value of A corresponding to this percentage is calculated and used in the calculations.

Losses to Follow-Up

The staggered patient entry over the accrual period results in censoring times ranging from *T* - *R* to *T* years during the follow-up period. This is often referred to as administrative censoring, since it is caused by the conclusion of the study rather than by some random factor working on an individual. To model the losses to follow-up in each group which come from other causes, we use the exponential distribution again, this time with hazard rates ω_1 and ω_2. You can obtain appropriate loss-to-follow-up hazard rates using the following formula or by using the Survival Parameter Conversion Tool available from the Tools menu or by pressing the small button to the rate of the loss-to-follow-up hazard rate box.

$$\omega = -\frac{\log\{1 - P_{loss}(R)\}}{R}$$

Example 1 – Finding the Power

A researcher is planning a clinical trial using a parallel, two-group, equal sample allocation design to compare the survivability of a new treatment with that of the current treatment. The proportion surviving one-year after the current treatment is 0.50 (h1 = 0.693). The power is desired when the proportion surviving in new treatment is 0.75 (h2 = 0.288).

The trial will include a recruitment period of one-year after which participants will be followed for an additional two-years. It is assumed that patients will enter the study uniformly over the accrual period. The researcher estimates a loss-to-follow rate of 15% per year (ω1 = ω2 =0.165) in both the control and the experimental groups.

The researcher decides to investigate various sample sizes between 10 and 250 at the 0.05 significance level.

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	**Ha: h2 - h1 ≠ 0**
Alpha	**0.05**
Group Allocation	**Enter total sample size and percentage in Group 1**
Total Sample Size (N)	**10 25 50 100 150 200 250**
Percent in Group 1	**50**
ω1 (Loss Hazard Rate of Control Group)	**0.165**
ω2 (Loss Hazard Rate of Treatment Group)	**ω1**
R (Accrual, or Recruitment, Time)	**1**
Percent of R Until 50% are Accrued	**50**
T-R (Follow-Up Time)	**2**
Specify Hazard Parameters Using	**Rates**
h1 (Hazard Rate of Control Group)	**0.693**
h2 (Hazard Rate of Treatment Group)	**0.288**

Output

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

Numeric Reports

Numeric Results

Solve For: Power
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: h2 - h1 = 0 vs. Ha: h2 - h1 ≠ 0
Accrual: Uniform

	Sample Size			Hazard Rate		Hazard Rate Difference	Hazard Ratio	Loss Hazard Rate		Time			
Power	N	N1	N2	h1	h2	D	HR	ω1	ω2	Accrual R	Follow-Up T - R	Alpha	Report Row
0.1614	10	5	5	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	1
0.3291	25	12	13	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	2
0.5838	50	25	25	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	3
0.8668	100	50	50	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	4
0.9642	150	75	75	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	5
0.9914	200	100	100	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	6
0.9981	250	125	125	0.693	0.288	-0.405	0.416	0.165	0.165	1	2	0.05	7

	Number of Events			Percent Group 1	Event Probability		Variance		Report
Power	E	E1	E2	%N1	Pr(E1)	Pr(E2)	σ²(h1)	σ²(h2)	Row
0.1614	5.7	3.6	2.1	50	0.71	0.429	0.676	0.193	1
0.3291	14.1	8.5	5.6	50	0.71	0.429	0.676	0.193	2
0.5838	28.5	17.8	10.7	50	0.71	0.429	0.676	0.193	3
0.8668	57.0	35.5	21.5	50	0.71	0.429	0.676	0.193	4
0.9642	85.5	53.3	32.2	50	0.71	0.429	0.676	0.193	5
0.9914	113.9	71.0	42.9	50	0.71	0.429	0.676	0.193	6
0.9981	142.4	88.8	53.6	50	0.71	0.429	0.676	0.193	7

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N, N1, and N2	The sample sizes of both, the control, and the treatment groups, respectively.
h1 and h2	The hazard rates in the control and treatment groups, respectively.
D	The difference in hazard rates. D = h2 - h1.
HR	The hazard ratio. HR = h2 / h1.
ω1 and ω2	The rates at which subjects in groups 1 and 2 are lost to follow up, respectively.
R	The accrual (recruitment) time.
T - R	The follow-up time. Hence, T is the total time of the study.
Alpha	The probability of rejecting a true null hypothesis.
E, E1, and E2	The number of events required in both, the control, and the treatment groups, respectively.
%N1	The percent of the total sample that is in group 1, the control group. %N1 = 100 x N1 / N.
Pr(E1) and Pr(E2)	The probabilities of an event in the control and treatment groups, respectively.
σ²(h1) and σ²(h2)	The variances of the estimates of h1 and h2, respectively.

Summary Statements

A parallel, two-group design will be used to test whether the Group 2 (treatment) hazard rate is different from the Group 1 (control) hazard rate (H0: h2 = h1 versus Ha: h2 ≠ h1). The comparison will be made using a two-sided, two-sample maximum likelihood estimation Z test with a Type I error rate (α) of 0.05. Patients will enter the study during an accrual period of 1 time period. 50% of the enrollment will be complete when 50% of the accrual time has passed (uniform accrual). A follow-up period of 2 time periods will have a 0.165 loss to follow-up hazard rate in the control group and a 0.165 loss to follow-up hazard rate in the treatment group. The calculations are based on the assumption that the survival times are exponentially distributed. To detect a hazard rate difference of -0.405 (h1 = 0.693, h2 = 0.288), with a sample size of 5 subjects in Group 1 and 5 subjects in Group 2 (totaling 10 subjects), the power is 0.1614. The corresponding number of events is 3.6 in Group 1 and 2.1 in Group 2 (totaling 5.7 events).

References

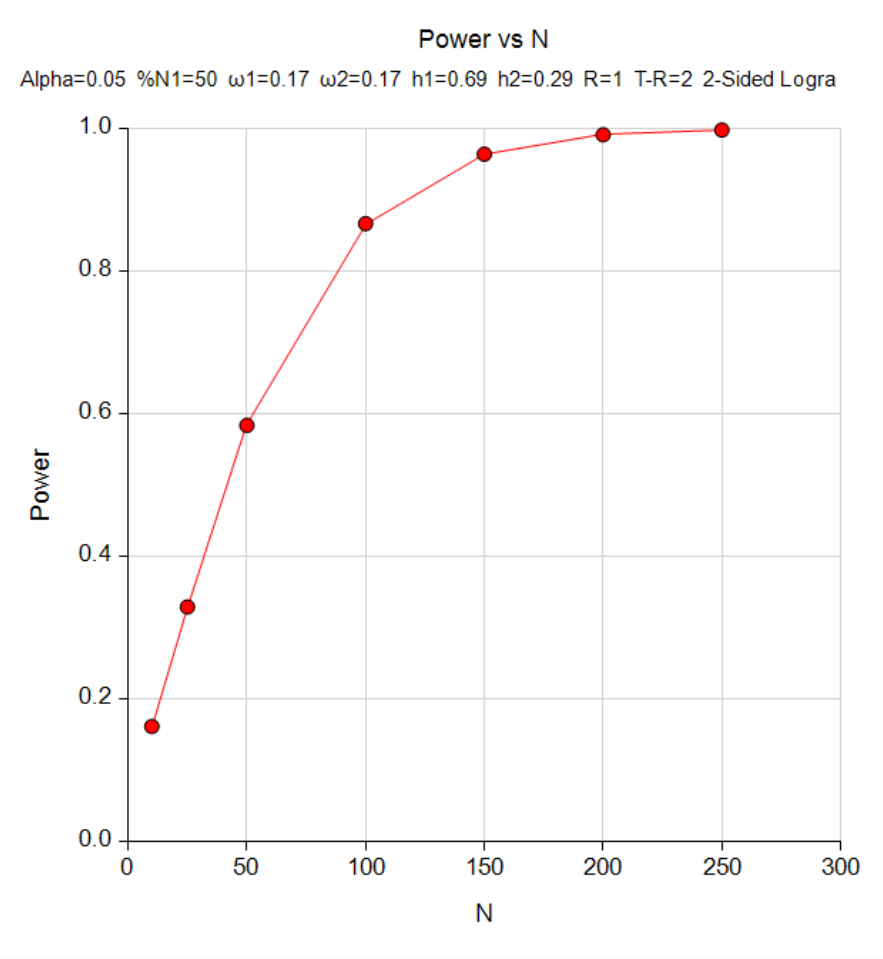
Chow, S.C., Shao, J., Wang, H. 2008. Sample Size Calculations in Clinical Research, 2nd Edition. Chapman & Hall/CRC.

Lachin, John M. and Foulkes, Mary A. 1986. 'Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics, Volume 42, September, pages 507-516.

These reports show the values of each of the parameters, one scenario per row. The second report presents information about the number of events that are necessary.

Plots Section

Plots



This plot shows the relationship between power and sample size.

Example 2 – Finding the Sample Size

Continuing with the previous example, the researcher wants to investigate the sample size necessary to achieve 90% power for treatment hazard rates of 0.55 to 0.80 at the 0.05 significance level. The follow-up times are 1, 2, and 3 years. All other parameters will remain the same.

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	**Ha: h2 - h1 ≠ 0**
Power	**0.90**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
ω1 (Loss Hazard Rate of Control Group)	**0.165**
ω2 (Loss Hazard Rate of Treatment Group)	**ω1**
R (Accrual, or Recruitment, Time)	**1**
Percent of R Until 50% are Accrued	**50**
T-R (Follow-Up Time)	**1 2 3**
Specify Hazard Parameters Using	**Rates**
h1 (Hazard Rate of Control Group)	**0.693**
h2 (Hazard Rate of Treatment Group)	**0.1 to 0.5 by 0.1**

Output

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

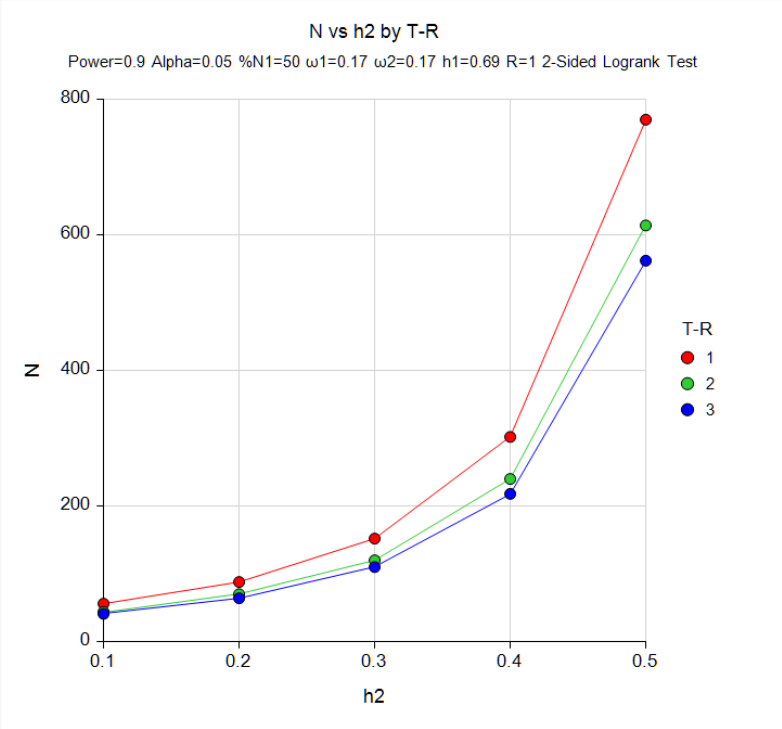
Numeric Results

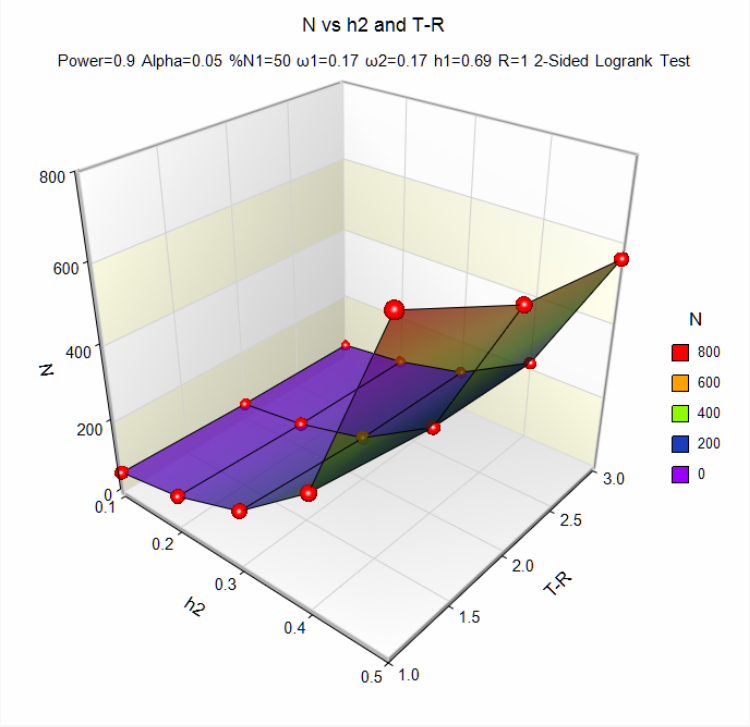
Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: h2 - h1 = 0 vs. Ha: h2 - h1 ≠ 0
Accrual: Uniform

	Sample Size			Hazard Rate		Hazard Rate Difference	Hazard Ratio	Loss Hazard Rate		Time			
Power	N	N1	N2	h1	h2	D	HR	ω1	ω2	Accrual R	Follow-Up T - R	Alpha	Report Row
0.9074	56	28	28	0.693	0.1	-0.593	0.144	0.165	0.165	1	1	0.05	1
0.9020	44	22	22	0.693	0.1	-0.593	0.144	0.165	0.165	1	2	0.05	2
0.9004	41	20	21	0.693	0.1	-0.593	0.144	0.165	0.165	1	3	0.05	3
0.9034	88	44	44	0.693	0.2	-0.493	0.289	0.165	0.165	1	1	0.05	4
0.9038	70	35	35	0.693	0.2	-0.493	0.289	0.165	0.165	1	2	0.05	5
0.9046	64	32	32	0.693	0.2	-0.493	0.289	0.165	0.165	1	3	0.05	6
0.9014	152	76	76	0.693	0.3	-0.393	0.433	0.165	0.165	1	1	0.05	7
0.9006	120	60	60	0.693	0.3	-0.393	0.433	0.165	0.165	1	2	0.05	8
0.9027	110	55	55	0.693	0.3	-0.393	0.433	0.165	0.165	1	3	0.05	9
0.9007	302	151	151	0.693	0.4	-0.293	0.577	0.165	0.165	1	1	0.05	10
0.9012	240	120	120	0.693	0.4	-0.293	0.577	0.165	0.165	1	2	0.05	11
0.9003	218	109	109	0.693	0.4	-0.293	0.577	0.165	0.165	1	3	0.05	12
0.9002	770	385	385	0.693	0.5	-0.193	0.722	0.165	0.165	1	1	0.05	13
0.9000	614	307	307	0.693	0.5	-0.193	0.722	0.165	0.165	1	2	0.05	14
0.9001	562	281	281	0.693	0.5	-0.193	0.722	0.165	0.165	1	3	0.05	15

	Number of Events			Percent Group 1	Event Probability		Variance		Report
Power	E	E1	E2	%N1	Pr(E1)	Pr(E2)	σ²(h1)	σ²(h2)	Row
0.9074	19.6	16.2	3.4	50	0.578	0.123	0.831	0.081	1
0.9020	19.6	15.6	4.0	50	0.710	0.182	0.676	0.055	2
0.9004	20.1	15.3	4.8	50	0.766	0.228	0.627	0.044	3
0.9034	35.5	25.4	10.1	50	0.578	0.229	0.831	0.174	4
0.9038	36.3	24.9	11.4	50	0.710	0.327	0.676	0.122	5
0.9046	37.1	24.5	12.6	50	0.766	0.394	0.627	0.101	6
0.9014	68.3	43.9	24.4	50	0.578	0.321	0.831	0.280	7
0.9006	69.1	42.6	26.5	50	0.710	0.442	0.676	0.204	8
0.9027	70.6	42.1	28.5	50	0.766	0.517	0.627	0.174	9
0.9007	147.7	87.2	60.5	50	0.578	0.401	0.831	0.399	10
0.9012	149.2	85.2	64.0	50	0.710	0.533	0.676	0.300	11
0.9003	149.9	83.5	66.3	50	0.766	0.609	0.627	0.263	12
0.9002	403.2	222.4	180.7	50	0.578	0.469	0.831	0.533	13
0.9000	404.3	218.0	186.2	50	0.710	0.607	0.676	0.412	14
0.9001	405.6	215.3	190.3	50	0.766	0.677	0.627	0.369	15

Plots





This study shows the relative impact of changes in h2 and in T-R.

Example 3 – Validation using Chow et al. (2008)

Chow et al. (2008) page 172 presents an example of a parallel, two-group, equal sample allocation design to compare the hazard rates of a new treatment with that of the current treatment using a two-sided, logrank test. They want to compute the required sample size when h1 = 1 and h2 = 2 in a 3-year study with a 1-year, uniform accrual. Their example ignores loss-to-follow up in both groups. Alpha is set to 0.05 and power is 0.80.

They obtain a value of about 39 per group using extensive rounding in their calculations.

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**
Alternative Hypothesis	**Ha: h2 - h1 ≠ 0**
Power	**0.80**
Alpha	**0.05**
Group Allocation	**Equal (N1 = N2)**
ω1 (Loss Hazard Rate of Control Group)	**0**
ω2 (Loss Hazard Rate of Treatment Group)	**ω1**
R (Accrual, or Recruitment, Time)	**1**
Percent of R Until 50% are Accrued	**50**
T-R (Follow-Up Time)	**2**
Specify Hazard Parameters Using	**Rates**
h1 (Hazard Rate of Control Group)	**1**
h2 (Hazard Rate of Treatment Group)	**2**

Output

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

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: h2 - h1 = 0 vs. Ha: h2 - h1 ≠ 0
Accrual: Uniform

	Sample Size			Hazard Rate		Hazard Rate Difference	Hazard Ratio	Loss Hazard Rate		Time		
Power	N	N1	N2	h1	h2	D	HR	ω1	ω2	Accrual R	Follow-Up T - R	Alpha
0.8053	81	40	41	1	2	1	2	0	0	1	2	0.05

	Number of Events			Percent Group 1	Event Probability		Variance	
Power	E	E1	E2	%N1	Pr(E1)	Pr(E2)	$\sigma^2(h1)$	$\sigma^2(h2)$
0.8053	77.3	36.6	40.7	50	0.914	0.992	1.094	4.032

The value of 81 differs from Chow's 78 because of their extensive rounding to just two decimal places throughout their intermediate calculations.