

## Chapter 716

# Logrank Tests Accounting for Competing Risks

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## Introduction

Clinical trials are often designed to test the equality of two survival distributions. The two-sample t-test is not appropriate in this case because time-to-event data is usually not normally distributed and many individuals survive past the end of the study, resulting in *censored* observations. Instead, the logrank test is used to compare the two survival distributions because 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, and accounts for censoring.

When analyzing time-to-event data and calculating power and sample size, a complication arises when individuals in the study die from risk factors that are not directly related to the risk factor of interest. For example, a researcher may wish to determine if a new drug for some disease improves patient survival time when compared to a standard treatment. Therefore, the researchers would be interested to know how long each patient lives until he or she dies from the disease. However, during the course of the study, patients may also die from other risks such as myocardial infarction, diabetes, or even an accident. When a patient dies from one of these other risk factors, then the main event of interest cannot be observed, so the true time-to-event of the disease for that patient can never be determined. In this example the main *event of interest* would be death directly attributable to the disease. All of the other types of death are called *competing risks*.

When known, the power and sample size calculations should be adjusted to account for the competing risks. If the results are not adjusted, then the power calculated for the logrank test of the main event of interest may be grossly overestimated, depending on the incidence of competing risks (see Example 3e).

This procedure is based on the formulas presented in Pintilie (2006) and Machin et al. (2009), which are both based on the original paper Pintilie (2002). The power and sample size calculations in this module use the assumptions that time to event of interest and time to competing risk failure are independent and exponentially distributed. This module also assumes uniform accrual.

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## Technical Details

This section presents the power and sample size calculation method given in Pintilie (2006) and Machin et al. (2009), which are both based on the original paper Pintilie (2002).

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### Definitions

In this section we will define some of the often-used terms related to this module.

#### Cumulative Incidence

*Cumulative incidence* is defined as the probability that a particular event, such as the occurrence of a particular disease, will occur before a fixed time point,  $T_0$ . It can also be thought of as the proportion of individuals that experience an event (e.g., fail or die) before the time point,  $T_0$ . The cumulative incidence functions will be designated as  $F(T_0)$  in the formulas and discussions that follow.

#### Survival Proportion

The *survival proportion* represents the proportion of individuals that survive past a fixed time point,  $T_0$ . It can also be thought of as the probability that an individual will survive past the time point,  $T_0$ . The survival proportion for a given time point is often estimated using the non-parametric Kaplan-Meier curve. The survival function will be designated as  $S(T_0)$  in the formulas and discussions that follow.

#### Event of Interest

The *event of interest* refers to the risk factor that is of main concern in the trial or experiment. For example, in a study of cancer survival, the main event of interest would be death attributable directly to cancer. The event of interest will be denoted with a subscript  $ev$  in the formulas and discussions that follow.

#### Competing Risks

*Competing risks* refers to all other risk factors that may cause a subject to fail before the event of interest can be observed. For example, in a study of cancer survival, there are many other causes that may result in a patient's death such as accidents, heart disease, or diabetes. These other causes are called competing risks. Competing risks will be denoted with a subscript  $cr$  in the formulas and discussions that follow.

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### Assumptions

The power and sample size calculations in the module for the logrank test are based on the following assumptions:

1. Failure times for the event of interest and competing risks are independent.
2. Failure times are exponentially distributed.
3. Uniform entry of subjects into the trial during the accrual period.

## The Cumulative Incidence Function

In the absence of competing risks and under the exponential assumption, the cumulative incidence function for the event of interest in group  $i$  at time  $T0$  is given as

$$F_{ev,i}(T0) = 1 - \exp\{-T0 \times h_{ev,i}\},$$

where  $h_{ev,i}$  is the hazard rate for the event of interest in group  $i$ . Notice that in the absence of competing risks

$$F_{ev,i}(T0) = 1 - S_{ev,i}(T0),$$

where  $S_{ev,i}(T0)$  is the cumulative survival function as defined below. In the presence of competing risks, the cumulative incidence function for the event of interest in group  $i$  at time  $T0$  is

$$F_{ev,i}(T0) = \frac{h_{ev,i}}{h_{ev,i} + h_{cr,i}} (1 - \exp\{-T0 \times (h_{ev,i} + h_{cr,i})\})$$

where  $h_{cr,i}$  is the hazard rate for competing risks in group  $i$ . The cumulative incidence function for competing risks in group  $i$  at time  $T0$  is

$$F_{cr,i}(T0) = \frac{h_{cr,i}}{h_{ev,i} + h_{cr,i}} (1 - \exp\{-T0 \times (h_{ev,i} + h_{cr,i})\})$$

By solving this system of equations, the hazard rates in group  $i$  are calculated from the cumulative incidences as

$$h_{ev,i} = F_{ev,i}(T0) \times \left( \frac{-\ln(1 - F_{ev,i}(T0) - F_{cr,i}(T0))}{T0 \times (F_{ev,i}(T0) + F_{cr,i}(T0))} \right)$$

$$h_{cr,i} = F_{cr,i}(T0) \times \left( \frac{-\ln(1 - F_{ev,i}(T0) - F_{cr,i}(T0))}{T0 \times (F_{ev,i}(T0) + F_{cr,i}(T0))} \right)$$

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## The Cumulative Survival Function

Under the exponential distribution assumption, the cumulative survival functions for the event of interest and competing risks in group  $i$  at time  $T0$  are

$$S_{ev,i}(T0) = \exp\{-T0 \times h_{ev,i}\}$$

$$S_{cr,i}(T0) = \exp\{-T0 \times h_{cr,i}\},$$

where  $h_{ev,i}$  is the hazard rate for the event of interest in group  $i$  and  $h_{cr,i}$  is the hazard rate for competing risks in group  $i$ . The cumulative survival function is often estimated non-parametrically using the Kaplan-Meier curve.

The hazard rates for the event of interest and competing risks in group  $i$  are calculated from the cumulative survival functions as

$$h_{ev,i} = \left( \frac{-\ln(S_{ev,i}(T0))}{T0} \right)$$

$$h_{cr,i} = \left( \frac{-\ln(S_{cr,i}(T0))}{T0} \right)$$

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## Hazard Ratio

The hazard ratio used in power calculations is calculated from the hazard rates for the event of interest as

$$HR = \left( \frac{h_{ev,2}}{h_{ev,1}} \right)$$

the hazard rate for the treatment group divided by the hazard rate for the control group. The hazard rates may be calculated using cumulative survival proportions or cumulative incidences as described above.

## Probability of Event

With the hazard rates for the event of interest and competing risks, the probability of observing the event of interest in a subject in group  $i$ ,  $Pr_{ev,i}$ , is given as

$$Pr_{ev,i} = \frac{h_{ev,i}}{h_{ev,i} + h_{cr,i}} \left( 1 - \frac{\exp\{-(T - R) \times (h_{ev,i} + h_{cr,i})\} - \exp\{-T \times (h_{ev,i} + h_{cr,i})\}}{R \times (h_{ev,i} + h_{cr,i})} \right),$$

where  $T$  is the total time of trial and  $R$  is the accrual time. The follow-up time is calculated from  $T$  and  $R$  as

$$\text{Follow-Up Time} = T - R.$$

The overall probability of observing the event of interest during the study in both groups is given as

$$Pr_{ev} = p_1 Pr_{ev,1} + (1 - p_1) Pr_{ev,2},$$

where  $p_1$  is the proportion of subjects in group 1, the control group.

## Number of Events

When dealing with time-to-event data, it is the number of events observed, not the total number of subjects that is important to achieve the specified power. The total required number of events (for the event of interest),  $E$ , is calculated from the total sample size  $N$  and  $Pr_{ev}$  as

$$E = N \times Pr_{ev}.$$

The number of events in group  $i$  is calculated as

$$E_i = n_i \times Pr_{ev,i},$$

where  $n_i$  is the sample size for the  $i^{\text{th}}$  group.

## Logrank Test Statistic

The power and sample size formulas presented below are for the logrank test statistic, which is given by

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

where  $E$  is the number of events of the type of interest,  $Y_{ij}$  is the number of subjects at risk just prior to the  $j^{\text{th}}$  observed event in the  $i^{\text{th}}$  group, and  $I_k$  is a binary variable indicating whether the  $k^{\text{th}}$  event of the type of interest is from group 1 or not.  $L$  follows the standard normal distribution.

## Power Calculations

Assuming an exponential model and independence of failure times for the event of interest and competing risks, Pintilie (2006) gives the following equation relating  $E$  and power:

$$z_{1-\beta} = \sqrt{E \times p_1(1 - p_1)} \log(HR) - z_{1-\alpha/2}$$

with

- $\alpha$  probability of type I error
- $\beta$  probability of type II error
- $z_{1-\alpha/2}$  standard normal quantile for  $1 - \alpha/2$
- $z_{1-\beta}$  standard normal quantile for  $1 - \beta$
- $E$  total number of events for the risk factor of interest
- $p_1$  proportion of subjects in group 1, the control group
- $HR$  hazard ratio to detect

This power formula indicates that it is the total number of events observed, not the number of subjects that is critical for achieving the desired power for the logrank test.

## Sample Size

The power formula can be rearranged to solve for  $E$ , the total number of events required. The formula is

$$E = \left( \frac{1}{p_1(1 - p_1)} \right) \times \left( \frac{z_{1-\alpha/2} + z_{1-\beta}}{\log(HR)} \right)^2.$$

The overall sample size can be computed from  $E$  and  $Pr_{ev}$  as

$$N = \frac{E}{Pr_{ev}} = \left( \frac{1}{p_1(1 - p_1) \times Pr_{ev}} \right) \times \left( \frac{z_{1-\alpha/2} + z_{1-\beta}}{\log(HR)} \right)^2.$$

The individual group sample sizes are calculated as

$$n_1 = N \times p_1,$$

$$n_2 = N \times (1 - p_1),$$

where  $p_1$  is the proportion of subjects in group 1, the control group.

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## Loss to Follow-Up

For most studies, a certain proportion of the individuals that are recruited for the study will drop out and will be lost to subsequent follow-up. These individuals will never contribute events to the study and must be considered censored just as those who finish the study without ever having experienced an event. The sample size must be adjusted to account for these individuals in order to calculate the correct power for the study. The adjusted sample size formula is given by

$$N_{adjusted} = \frac{N}{(1 - W)},$$

where  $W$  is the proportion lost to follow-up. When solving for power or maximum effect size, this adjustment is applied to the sample size entered before the power is computed. Therefore, the sample size that is actually used to calculate power or effect size is

$$N_{used} = N_{entered} \times (1 - W).$$

When solving for sample size, this adjustment is made after the required sample size is computed so the sample size that is actually returned is  $N_{adjusted}$ , which is larger than the sample size that would be required if no individuals were lost to follow-up. When there is no loss to follow-up, then  $W = 0$ ,  $N_{adjusted} = N$ , and  $N_{used} = N_{entered}$ .

## Example 1 – Finding the Power

A group of researchers is planning a clinical trial using a parallel, two-group, equal sample allocation design to compare the survivability from a new treatment for a particular disease with that of the current treatment. They have information about the cumulative incidences for the disease and competing risk factors. The cumulative incidence for the disease under the current treatment is 0.10 after 3 years. They want to find the power for a logrank test if the cumulative incidence is reduced by 50% under the new treatment, so the treatment cumulative incidence is 0.05 after 3 years. The cumulative incidence from competing risks is 0.65 after 3 years for both groups.

The trial will include a recruitment period of 4 years, after which participants will be followed for an additional 3 years. The researchers estimate a loss to follow-up rate of 10% over the entire study.

The researchers decide to investigate sample sizes between 100 and 900 at a significance level of 0.05.

### 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>100 to 900 by 100</b>
Percent in Group 1 .....	<b>50</b>
W (Proportion Lost to Follow-Up).....	<b>0.1</b>
R (Accrual Time).....	<b>4</b>
T-R (Follow-Up Time) .....	<b>3</b>
Specify the Hazard Ratio Using .....	<b>Cumulative Incidences</b>
T0 (Fixed Time Point) .....	<b>3</b>
Fev1(T0) (Control) .....	<b>0.10</b>
Fev2(T0) (Treatment).....	<b>0.05</b>
Fcr1(T0) (Control) .....	<b>0.65</b>
Fcr2(T0) (Treatment) .....	<b>0.65</b>



# Output

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

## Numeric Reports

### Numeric Results

Solve For: [Power](#)  
 Hypothesis: Two-Sided  
 Groups: 1 = Control, 2 = Treatment  
 T0 (Fixed Time Point): 3  
 W (Proportion Lost to Follow-Up): 0.1

Power	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Cumulative Incidence				Time		Alpha	Report Row
	N	N1	N2			Event of Interest		Competing Risks		Accrual R	Follow-Up T - R		
						Fev1	Fev2	Fcr1	Fcr2				
0.19094	100	50	50	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	1
0.33549	200	100	100	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	2
0.46820	300	150	150	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	3
0.58358	400	200	200	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	4
0.67986	500	250	250	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	5
0.75772	600	300	300	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	6
0.81912	700	350	350	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	7
0.86657	800	400	400	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	8
0.90261	900	450	450	0.5	0.4653	0.1	0.05	0.65	0.65	4	3	0.05	9

Power	Number of Events			Probability of an Event			Event of Interest		Competing Risks		Report Row
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2	
0.19094	8.1	5.3	2.7	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	1
0.33549	16.1	10.6	5.5	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	2
0.46820	24.2	15.9	8.2	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	3
0.58358	32.2	21.3	10.9	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	4
0.67986	40.3	26.6	13.7	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	5
0.75772	48.3	31.9	16.4	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	6
0.81912	56.4	37.2	19.1	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	7
0.86657	64.4	42.5	21.9	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	8
0.90261	72.5	47.8	24.6	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727	9

- T0 The base time at which the cumulative incidences are calculated.
- W The proportion of the individuals lost to follow-up during the entire study.
- Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
- N The total sample size of both groups combined.
- N1 and N2 The sample sizes for the control and treatment groups, respectively.
- p1 The proportion of the total sample size (N) that is assigned to the control group.
- HR The hazard ratio (hev2/hev1), the treatment group's hazard rate divided by the control group's hazard rate for the event of interest.
- Fev1 and Fev2 The cumulative incidences at time T0 for the event of interest in the control and treatment groups, respectively.
- Fcr1 and Fcr2 The cumulative incidences at time T0 for the competing risk factors in the control and treatment groups, respectively.
- R The accrual or entry time for the study.
- T - R The follow-up time for the study. T is the total time.
- Alpha The probability of rejecting a true null hypothesis.
- E The total number of events required for the study.
- E1 and E2 The number of events required for the control and treatment groups, respectively.
- Pr(ev) The overall probability of observing the event of interest during the study.
- Pr(ev1) and Pr(ev2) The probability of observing the event of interest in a subject during the study for the control and treatment groups, respectively.
- hev1 and hev2 The hazard rates for the event of interest in the control and treatment groups, respectively.
- hcr1 and hcr2 The hazard rates for the competing risk factors in the control and treatment groups, respectively.
- Report Row A line number assigned to allow corresponding report lines to be identified.

## Logrank Tests Accounting for Competing Risks

### Summary Statements

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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. The comparison will be made using a two-sided, two-sample logrank test accounting for competing risks, with a Type I error rate ( $\alpha$ ) of 0.05. The total duration of the study will be 7 time periods with an accrual (entry) time of 4 periods and a follow-up time of 3 periods. The proportion of subjects lost to follow-up during the entire study is 0.1. To detect the event of interest cumulative incidence proportions (in a time of 3) of 0.05 in the treatment group and 0.1 in the control group (a hazard ratio of 0.4653), with competing risks cumulative incidence proportions (in a time of 3) of 0.65 in the treatment group and 0.65 in the control group, with a sample size of 50 subjects in Group 1 and 50 subjects in Group 2 (totaling 100 subjects), the power is 0.19094. The corresponding number of events is 5.3 in Group 1 and 2.7 in Group 2 (totaling 8.1 events).

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### References

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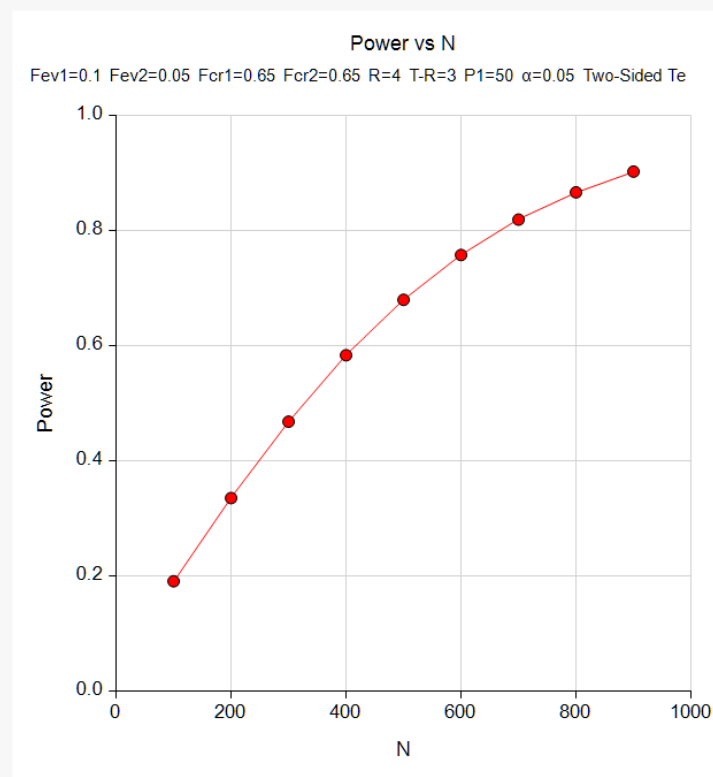
- Machin, D., Campbell, M.J., Tan, S.B., Tan, S.H. 2009. Sample Size Tables for Clinical Studies, Third Edition. Wiley-Blackwell, Chichester, United Kingdom.
- Pintilie, M., 2006. Competing Risks: A Practical Perspective. John Wiley & Sons, Chichester, United Kingdom.
- Pintilie, M., 2002. 'Dealing with Competing Risks: Testing Covariates and Calculating Sample Size'. Statistics in Medicine, Volume 21, pages 3317-3324.
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These reports show the values of each of the parameters, one scenario per row. The second section of the report presents information about the number of events that are required.

## Plots Section

### Plots

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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 hazard ratios between 0.4 and 0.8 at the 0.05 significance level. The follow-up times are 2, 3, and 5 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 .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
W (Proportion Lost to Follow-Up).....	<b>0.1</b>
R (Accrual Time).....	<b>4</b>
T-R (Follow-Up Time) .....	<b>2 3 5</b>
Specify the Hazard Ratio Using .....	<b>Control Cumulative Incidences and Hazard Ratio</b>
T0 (Fixed Time Point) .....	<b>3</b>
Fev1(T0) (Control) .....	<b>0.10</b>
HR (Hazard Ratio = hev2 / hev1).....	<b>0.4 to 0.8 by 0.1</b>
Fcr1(T0) (Control) .....	<b>0.65</b>

# Output

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

## Numeric Results

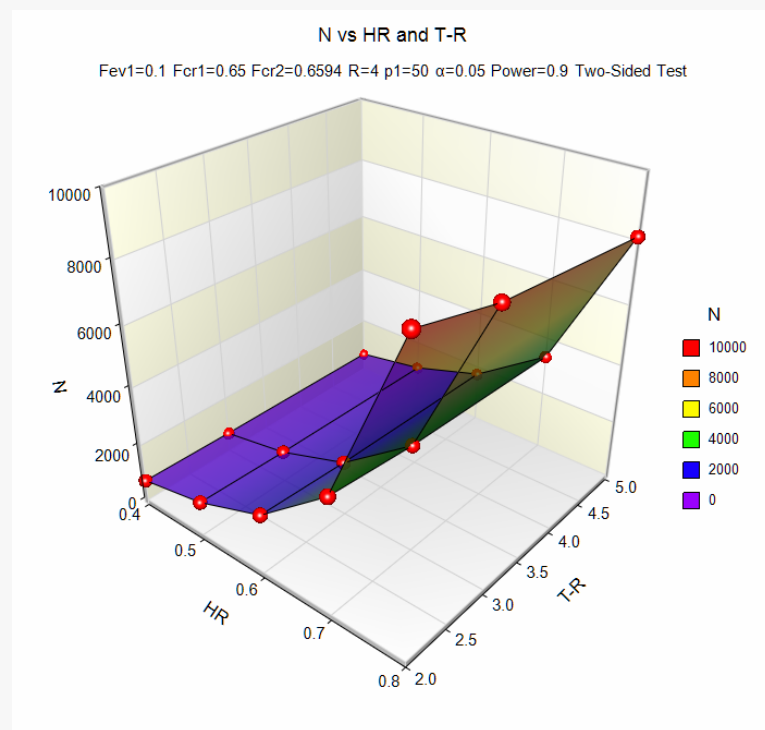
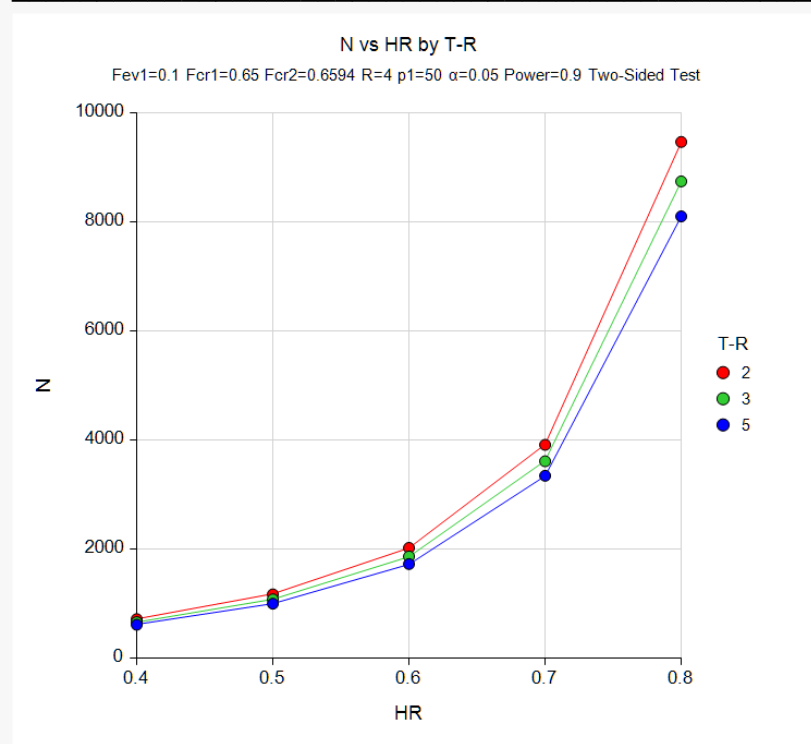
Solve For: [Sample Size](#)  
 Hypothesis: Two-Sided  
 Groups: 1 = Control, 2 = Treatment  
 T0 (Fixed Time Point): 3  
 W (Proportion Lost to Follow-Up): 0.1

Power	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Cumulative Incidence				Time			Report Row
	N	N1	N2			Event of Interest		Competing Risks		Accrual R	Follow-Up T - R	Alpha	
						Fev1	Fev2	Fcr1	Fcr2				
0.90010	717	358	359	0.5	0.4	0.1	0.0418	0.65	0.6789	4	2	0.05	1
0.90010	662	331	331	0.5	0.4	0.1	0.0418	0.65	0.6789	4	3	0.05	2
0.90038	613	306	307	0.5	0.4	0.1	0.0418	0.65	0.6789	4	5	0.05	3
0.90022	1170	585	585	0.5	0.5	0.1	0.0518	0.65	0.6740	4	2	0.05	4
0.90008	1079	539	540	0.5	0.5	0.1	0.0518	0.65	0.6740	4	3	0.05	5
0.90026	999	499	500	0.5	0.5	0.1	0.0518	0.65	0.6740	4	5	0.05	6
0.90014	2023	1011	1012	0.5	0.6	0.1	0.0618	0.65	0.6691	4	2	0.05	7
0.90006	1866	933	933	0.5	0.6	0.1	0.0618	0.65	0.6691	4	3	0.05	8
0.90005	1727	863	864	0.5	0.6	0.1	0.0618	0.65	0.6691	4	5	0.05	9
0.90006	3913	1956	1957	0.5	0.7	0.1	0.0715	0.65	0.6642	4	2	0.05	10
0.90004	3612	1806	1806	0.5	0.7	0.1	0.0715	0.65	0.6642	4	3	0.05	11
0.90007	3345	1672	1673	0.5	0.7	0.1	0.0715	0.65	0.6642	4	5	0.05	12
0.90001	9468	4734	4734	0.5	0.8	0.1	0.0812	0.65	0.6594	4	2	0.05	13
0.90001	8744	4372	4372	0.5	0.8	0.1	0.0812	0.65	0.6594	4	3	0.05	14
0.90002	8103	4051	4052	0.5	0.8	0.1	0.0812	0.65	0.6594	4	5	0.05	15

Power	Number of Events			Probability of an Event			Hazard Rate				Report Row
	E	E1	E2	Pr(ev)	Event of Interest		Competing Risks				
					Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2	
0.90010	50.1	35.2	14.9	0.0776	0.1092	0.0461	0.0616	0.0246	0.4005	0.4005	1
0.90010	50.1	35.1	14.9	0.0842	0.1181	0.0502	0.0616	0.0246	0.4005	0.4005	2
0.90038	50.1	35.1	15.1	0.0910	0.1273	0.0546	0.0616	0.0246	0.4005	0.4005	3
0.90022	87.5	57.5	30.0	0.0831	0.1092	0.0571	0.0616	0.0308	0.4005	0.4005	4
0.90008	87.5	57.4	30.1	0.0901	0.1181	0.0621	0.0616	0.0308	0.4005	0.4005	5
0.90026	87.6	57.2	30.3	0.0974	0.1273	0.0675	0.0616	0.0308	0.4005	0.4005	6
0.90014	161.1	99.4	61.8	0.0885	0.1092	0.0679	0.0616	0.0370	0.4005	0.4005	7
0.90006	161.1	99.2	61.9	0.0960	0.1181	0.0738	0.0616	0.0370	0.4005	0.4005	8
0.90005	161.1	98.9	62.2	0.1037	0.1273	0.0800	0.0616	0.0370	0.4005	0.4005	9
0.90006	330.4	192.3	138.2	0.0939	0.1092	0.0785	0.0616	0.0431	0.4005	0.4005	10
0.90004	330.4	192.0	138.4	0.1017	0.1181	0.0852	0.0616	0.0431	0.4005	0.4005	11
0.90007	330.5	191.6	138.9	0.1098	0.1273	0.0923	0.0616	0.0431	0.4005	0.4005	12
0.90001	844.1	465.3	378.8	0.0991	0.1092	0.0889	0.0616	0.0493	0.4005	0.4005	13
0.90001	844.1	464.8	379.3	0.1073	0.1181	0.0964	0.0616	0.0493	0.4005	0.4005	14
0.90002	844.2	464.1	380.0	0.1158	0.1273	0.1042	0.0616	0.0493	0.4005	0.4005	15

Logrank Tests Accounting for Competing Risks

Plots



This study shows the relative impact of changes in hazard ratio and T-R on sample size for 90% power.

## Example 3a – Validation 1 using Pintilie (2006)

Pintilie (2006) page 122-124 presents a series of examples related to calculating power for testing a new drug expected to have selective toxicity for hypoxic cancer cells. The new drug is important because previous studies had shown that patients with a hypoxic tumor were more likely to experience a failure than those whose tumor was not hypoxic. A two-group, randomized study will be used to test the new drug.

They wish to detect a hazard ratio of 0.5. (The book specifically says that they want to detect a hazard ratio of 2, but they define HR as  $hev1/hev2$ . **PASS** defines hazard ratio as  $HR = hev2/hev1$  so we'll use the value  $1/2 = 0.5$  for HR.) The test will be performed at a 0.05 significance level with a control survival proportion of 0.5 at 3 years for the main event of interest and 0.4 at 3 years for competing risks. The accrual time is 3 years, and the follow-up time is 2 years. The sample size is 150 since they expect to enroll 50 individuals per year during the accrual period.

They report that the power for this calculation is 0.6162274.

### 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 3a** 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>150</b>
Percent in Group 1 .....	<b>50</b>
W (Proportion Lost to Follow-Up).....	<b>0</b>
R (Accrual Time).....	<b>3</b>
T-R (Follow-Up Time) .....	<b>2</b>
Specify the Hazard Ratio Using .....	<b>Control Survival Proportions and Hazard Ratio</b>
T0 (Fixed Time Point) .....	<b>3</b>
Sev1(T0) (Control) .....	<b>0.5</b>
HR (Hazard Ratio = $hev2 / hev1$ ).....	<b>0.5</b>
Scr1(T0) (Control).....	<b>0.4</b>

#### Reports Tab

Power and Beta Decimals.....	<b>7</b>
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## Logrank Tests Accounting for Competing Risks

## Output

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

## Numeric Results

Solve For: [Power](#)  
 Hypothesis: Two-Sided  
 Groups: 1 = Control, 2 = Treatment  
 T0 (Fixed Time Point): 3  
 W (Proportion Lost to Follow-Up): 0.0

Power	Cumulative Incidence												Report Row
	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Event of Interest		Competing Risks		Time		Alpha	
	N	N1	N2			Fev1	Fev2	Fcr1	Fcr2	Accrual R	Follow-Up T - R		
0.6162274	150	75	75	0.5	0.5	0.5	0.7071	0.4	0.4	3	2	0.05	1

Power	Hazard Rate											Report Row
	Number of Events			Probability of an Event			Event of Interest		Competing Risks			
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2		
0.6162274	42.4	26.8	15.5	0.2824	0.3575	0.2073	0.231	0.1155	0.3054	0.3054	1	

The value of 0.6162274 calculated by **PASS** is exactly the same as the value for power reported by Pintilie (2006).

## Example 3b – Validation 2 using Pintilie (2006)

Following the previous validation example, Pintilie (2006) presents results for calculating power under the same circumstances, except they use cumulative incidences instead of survival proportions. The cumulative incidence values are 0.345 at 3 years for the event of interest in the control group and 0.455 at 3 years for competing risks in the control group. All other parameters stay the same.

They report that the power for this calculation is 0.6168332.

### 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 3b** 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>150</b>
Percent in Group 1 .....	<b>50</b>
W (Proportion Lost to Follow-Up).....	<b>0</b>
R (Accrual Time).....	<b>3</b>
T-R (Follow-Up Time) .....	<b>2</b>
Specify the Hazard Ratio Using .....	<b>Control Cumulative Incidences and Hazard Ratio</b>
T0 (Fixed Time Point) .....	<b>3</b>
Fev1(T0) (Control) .....	<b>0.345</b>
HR (Hazard Ratio = hev2 / hev1).....	<b>0.5</b>
Fcr1(T0) (Control) .....	<b>0.455</b>

#### Reports Tab

Power and Beta Decimals.....	<b>7</b>
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## Logrank Tests Accounting for Competing Risks

## Output

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

## Numeric Results

Solve For: [Power](#)  
 Hypothesis: Two-Sided  
 Groups: 1 = Control, 2 = Treatment  
 T0 (Fixed Time Point): 3  
 W (Proportion Lost to Follow-Up): 0.0

Power	Cumulative Incidence												Report Row
	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Event of Interest		Competing Risks		Time			
	N	N1	N2			Fev1	Fev2	Fcr1	Fcr2	Accrual R	Follow-Up T - R	Alpha	
0.6168332	150	75	75	0.5	0.5	0.345	0.1971	0.455	0.5199	3	2	0.05	1

Power	Hazard Rate										Report Row
	Number of Events			Probability of an Event			Event of Interest		Competing Risks		
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2	
0.6168332	42.4	26.8	15.6	0.2828	0.3579	0.2076	0.2314	0.1157	0.3051	0.3051	1

The value of 0.6168332 calculated by **PASS** is exactly the same as the value for power reported by Pintilie (2006).

## Example 3c – Validation 3 using Pintilie (2006)

Following the previous validation examples, Pintilie (2006) presents results for calculating power under the same circumstances, except for the expectation that the treatment will have an impact on competing risks. The survival proportions are 0.706 at 3 years for the event of interest in the treatment group and 0.3 at 3 years for competing risks in the treatment group. All other parameters stay the same as those in Example 3a.

They report that the power for this calculation is 0.5924636.

### 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 3c** 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>150</b>
Percent in Group 1 .....	<b>50</b>
W (Proportion Lost to Follow-Up).....	<b>0</b>
R (Accrual Time).....	<b>3</b>
T-R (Follow-Up Time) .....	<b>2</b>
Specify the Hazard Ratio Using .....	<b>Survival Proportions</b>
T0 (Fixed Time Point) .....	<b>3</b>
Sev1(T0) (Control) .....	<b>0.5</b>
Sev2(T0) (Treatment) .....	<b>0.706</b>
Scr1(T0) (Control).....	<b>0.4</b>
Scr2(T0) (Treatment) .....	<b>0.3</b>

#### Reports Tab

Power and Beta Decimals.....	<b>7</b>
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## Logrank Tests Accounting for Competing Risks

## Output

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

## Numeric Results

Solve For: [Power](#)  
Hypothesis: Two-Sided  
Groups: 1 = Control, 2 = Treatment  
T0 (Fixed Time Point): 3  
W (Proportion Lost to Follow-Up): 0.0

Power	Cumulative Incidence												Report Row
	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Event of Interest		Competing Risks		Time		Alpha	
	N	N1	N2			Fev1	Fev2	Fcr1	Fcr2	Accrual R	Follow-Up T - R		
0.5924636	150	75	75	0.5	0.5023	0.5	0.706	0.4	0.3	3	2	0.05	1

Power	Hazard Rate										Report Row
	Number of Events			Probability of an Event			Event of Interest		Competing Risks		
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2	
0.5924636	40.6	26.8	13.8	0.2706	0.3575	0.1838	0.231	0.116	0.3054	0.4013	1

The value of 0.5924636 calculated by **PASS** is exactly the same as the value for power reported by Pintilie (2006).

## Example 3d – Validation 4 using Pintilie (2006)

Following the previous validation examples, Pintilie (2006) presents results for calculating power under the same circumstances with the expectation that the treatment will have an impact on competing risks. They now use cumulative incidences instead of survival proportions. The cumulative incidence values are 0.177 at 3 years for the event of interest in the treatment group and 0.61 at 3 years for competing risks in the treatment group. All other parameters stay the same as those in Example 3b.

They report that the power for this calculation is 0.5958667.

### 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 3d** 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>150</b>
Percent in Group 1 .....	<b>50</b>
W (Proportion Lost to Follow-Up).....	<b>0</b>
R (Accrual Time).....	<b>3</b>
T-R (Follow-Up Time) .....	<b>2</b>
Specify the Hazard Ratio Using .....	<b>Cumulative Incidences</b>
T0 (Fixed Time Point) .....	<b>3</b>
Fev1(T0) (Control) .....	<b>0.345</b>
Fev2(T0) (Treatment).....	<b>0.177</b>
Fcr1(T0) (Control) .....	<b>0.455</b>
Fcr2(T0) (Treatment) .....	<b>0.61</b>
Reports Tab	
Power and Beta Decimals.....	<b>7</b>

## Logrank Tests Accounting for Competing Risks

## Output

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

## Numeric Results

Solve For: [Power](#)  
Hypothesis: Two-Sided  
Groups: 1 = Control, 2 = Treatment  
T0 (Fixed Time Point): 3  
W (Proportion Lost to Follow-Up): 0.0

Power	Cumulative Incidence												Report Row
	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Event of Interest		Competing Risks		Time		Alpha	
	N	N1	N2			Fev1	Fev2	Fcr1	Fcr2	Accrual R	Follow-Up T - R		
0.5958667	150	75	75	0.5	0.5011	0.345	0.177	0.455	0.61	3	2	0.05	1

Power	Hazard Rate											Report Row
	Number of Events			Probability of an Event			Event of Interest		Competing Risks			
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2		
0.5958667	40.7	26.8	13.8	0.271	0.3579	0.1841	0.2314	0.1159	0.3051	0.3996	1	

The value of 0.5958667 calculated by **PASS** is exactly the same as the value for power reported by Pintilie (2006).

## Example 3e – Validation 5 using Pintilie (2006) – Ignoring Competing Risks

On page 124, Pintilie (2006) presents an example under the same conditions as Example 3c, except they now illustrate the effect of ignoring competing risks. To ignore the effect of competing risks, simply set the survival proportion for competing risks to one, meaning that nobody fails from competing risks. All other parameters remain the same.

They report that the power for this calculation is 0.7969974.

### 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 3e** 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 .....	<b>Power</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Enter total sample size and percentage in Group 1</b>
Total Sample Size (N).....	<b>150</b>
Percent in Group 1.....	<b>50</b>
W (Proportion Lost to Follow-Up).....	<b>0</b>
R (Accrual Time).....	<b>3</b>
T-R (Follow-Up Time) .....	<b>2</b>
Specify the Hazard Ratio Using .....	<b>Survival Proportions</b>
T0 (Fixed Time Point) .....	<b>3</b>
Sev1(T0) (Control) .....	<b>0.5</b>
Sev2(T0) (Treatment) .....	<b>0.706</b>
Scr1(T0) (Control).....	<b>1</b>
Scr2(T0) (Treatment) .....	<b>1</b>
Reports Tab	
Power and Beta Decimals.....	<b>7</b>

## Output

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

Numeric Results													
Solve For:	Power												
Hypothesis:	Two-Sided												
Groups:	1 = Control, 2 = Treatment												
T0 (Fixed Time Point):	3												
W (Proportion Lost to Follow-Up):	0.0												
Cumulative Incidence													
Power	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Event of Interest		Competing Risks		Time		Alpha	Report Row
	N	N1	N2			Fev1	Fev2	Fcr1	Fcr2	Accrual R	Follow-Up T - R		
0.7969974	150	75	75	0.5	0.5023	0.5	0.706	1	1	3	2	0.05	1
Hazard Rate													
Power	Number of Events			Probability of an Event			Event of Interest		Competing Risks		Report Row		
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2			
0.7969974	65.7	40.9	24.8	0.438	0.5456	0.3304	0.231	0.116	0	0	1		

The value of 0.7969974 calculated by **PASS** is exactly the same as the value for power reported by Pintilie (2006). Comparing this value to the value for power of 0.5924636 calculated in Example 3c, where competing risks were not ignored, we can see that the power can be grossly overestimated if competing risks are ignored.

## Example 4 – Validation using Machin et al. (2009) and Pintilie (2002)

Machin et al. (2009) presents an example originally used in Pintilie (2002) that calculates the sample size for an experiment designed to determine if the incidence of myocardial infarction (MI) in breast cancer survivors was affected by tangential radiation treatments, which were known to irradiate the heart when given to the left breast but not when given to the right. The incidence of competing risks in this patient population is large since only a small percentage lives long enough to experience MI, the event of interest.

The anticipated incidence of MI is 1.5% at 10 years for patients treated on the right (control) and 3% at 10 years for patients treated on the left (treatment). The incidence of competing risks was set at 68% at 10 years for both groups. Accrual is set at 9 years with 10 years of follow up. What sample size is required to achieve 80% power for a two-sided test with a significance level of 0.05?

Machin et al. (2009) and Pintilie (2002) report the following results:

N	2519 (Machin also reports a sample size of 2367 when not using rounded values)
hev1	0.00256
hev2	0.00523
hcr1	0.11618
hcr2	0.11856
HR	0.49 (calculated as hev1/hev2)
Pr(ev1)	0.01754
Pr(ev2)	0.03486
Pr(ev)	0.02620
E	65.3 (Machin also reports an event count of 62 when not using rounded values)

### 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 4a** 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 .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power.....	<b>0.80</b>
Alpha.....	<b>0.05</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
W (Proportion Lost to Follow-Up).....	<b>0</b>
R (Accrual Time).....	<b>9</b>
T-R (Follow-Up Time) .....	<b>10</b>
Specify the Hazard Ratio Using .....	<b>Cumulative Incidences</b>
T0 (Fixed Time Point) .....	<b>10</b>



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Fev1(T0) (Control) ..... **0.015**  
 Fev2(T0) (Treatment)..... **0.030**  
 Fcr1(T0) (Control) ..... **0.68**  
 Fcr2(T0) (Treatment) ..... **0.68**

Reports Tab

Incidence, Survival, HR, Hazard Rates

Decimals ..... **5**

## Output

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

### Numeric Results

Solve For: [Sample Size](#)  
 Hypothesis: Two-Sided  
 Groups: 1 = Control, 2 = Treatment  
 T0 (Fixed Time Point): 10  
 W (Proportion Lost to Follow-Up): 0.0

Power	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Cumulative Incidence				Time		Alpha	Report Row
	N	N1	N2			Event of Interest		Competing Risks		Accrual R	Follow-Up T - R		
						Fev1	Fev2	Fcr1	Fcr2				
0.80009	2355	1177	1178	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	1

Power	Number of Events			Probability of an Event			Event of Interest		Competing Risks		Report Row
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2	
0.80009	61.7	20.7	41.1	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	1

The sample size of 2355 calculated by **PASS** is slightly different from the value of 2519 calculated by Machin et al. (2009) and Pintilie (2002). The difference is due to rounding. Both round the hazard ratio to 0.5 (which would be 2 in **PASS**) before computing the sample size. The actual hazard ratio is 0.49 (which is 2.04089 in **PASS**), which results in a different sample size in **PASS**. The hazard rates and event probabilities calculated by **PASS** match those calculated by the authors exactly.

Machin et al. (2009) reports a second sample size of 2367 when not rounding the hazard ratio to 0.5. This is, again, slightly different from the sample size calculated by **PASS**. The difference here is due to the fact that Machin rounds the calculated number of events to 62 before computing the sample size, where **PASS** uses 61.7 to compute the sample size.

Logrank Tests Accounting for Competing Risks

You can load the settings file **Example 4b** to get the following results, solving for power.

**Numeric Results**

Solve For: [Power](#)  
 Hypothesis: Two-Sided  
 Groups: 1 = Control, 2 = Treatment  
 T0 (Fixed Time Point): 10  
 W (Proportion Lost to Follow-Up): 0.0

Power	Sample Size			Proportion in Group 1 p1	Hazard Ratio HR	Cumulative Incidence				Time		Alpha	Report Row
	N	N1	N2			Event of Interest		Competing Risks		Accrual R	Follow-Up T - R		
						Fev1	Fev2	Fcr1	Fcr2				
0.79993	2354	1177	1177	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	1
0.80009	2355	1177	1178	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	2
0.80026	2356	1178	1178	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	3
0.80192	2366	1183	1183	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	4
0.80208	2367	1183	1184	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	5
0.80225	2368	1184	1184	0.5	2.04089	0.015	0.03	0.68	0.68	9	10	0.05	6

Power	Number of Events			Probability of an Event			Event of Interest		Competing Risks		Report Row
	E	E1	E2	Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2	
0.79993	61.68	20.64	41.04	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	1
0.80009	61.71	20.65	41.05	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	2
0.80026	61.73	20.66	41.07	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	3
0.80192	61.99	20.75	41.24	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	4
0.80208	62.02	20.76	41.26	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	5
0.80225	62.05	20.77	41.28	0.0262	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	6

If you investigate a range of sample sizes around 2355 and 2367, you'll see that 2355 is the smallest sample size for which power is greater than or equal to 0.8. Furthermore, at a sample size of 2367 the required number of events is 62, the value used by Machin to arrive at their computed sample size. **PASS** does not round the number of events before computing the sample size.