

Chapter 716

Logrank Tests Accounting for Competing Risks

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.

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).

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.

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 T_0 is given as

$$F_{ev,i}(T_0) = 1 - \exp\{-T_0 \times h_{ev,i}\},$$

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

$$F_{ev,i}(T_0) = 1 - S_{ev,i}(T_0),$$

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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

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

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

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

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

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

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

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

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

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

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^{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^{th} observed event in the i^{th} group, and I_k is a binary variable indicating whether the k^{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

α	probability of type I error
β	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

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

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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.

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

$$N_{used} = N_{entered}.$$

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 *Power*, *Sample Size*, *Detectable Hazard Ratio (HR < 1)*, or *Detectable Hazard Ratio (HR > 1)*.

Test

Alternative Hypothesis

Specify whether to make calculations for a one-sided or a two-sided test. When you select a two-sided alternative hypothesis, the value for alpha is divided by 2.

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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. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal survival curves when in fact the curves are different.

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 also commonly used.

You may enter a single value such as *0.8* or a range of values such as *0.8 0.9 0.95* or *0.8 to 0.95 by 0.05*.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when you reject the null hypothesis of equal survival curves when in fact the curves are equal.

Values of alpha must be between zero and one. Historically, the value of 0.05 has been used for alpha. 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 single value such as *0.05* or a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size (When Solving for Sample Size)

Group Allocation

Select the option that describes the constraints on $N1$ or $N2$ or both.

The options are

- **Equal ($N1 = N2$)**

This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.

- **Enter $R = N2/N1$, solve for $N1$ and $N2$**

For this choice, you set a value for the ratio of $N2$ to $N1$, and then PASS determines the needed $N1$ and $N2$, with this ratio, to obtain the desired power. An equivalent representation of the ratio, R , is

$$N2 = R * N1.$$

- **Enter percentage in Group 1, solve for $N1$ and $N2$**

For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed $N1$ and $N2$ with this percentage to obtain the desired power.

R (Group Sample Size Ratio)

This option is displayed only if Group Allocation = "Enter $R = N2/N1$, solve for $N1$ and $N2$."

R is the ratio of $N2$ to $N1$. That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of $N2$ to $N1$ while solving for $N1$ and $N2$. Only sample size combinations with this ratio are considered.

$N2$ is related to $N1$ by the formula:

$$N2 = [R \times N1],$$

where the value $[Y]$ is the next integer $\geq Y$.

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For example, setting $R = 2.0$ results in a Group 2 sample size that is double the sample size in Group 1 (e.g., $N1 = 10$ and $N2 = 20$, or $N1 = 50$ and $N2 = 100$).

R must be greater than 0. If $R < 1$, then $N2$ will be less than $N1$; if $R > 1$, then $N2$ will be greater than $N1$. You can enter a single or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for N1 and N2."

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for $N1$ and $N2$. Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

W (Proportion Lost to Follow-Up)

This is the proportion of subjects that are lost to follow-up. The sample size is adjusted to account for this loss using the formula

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

where W is the proportion lost to follow-up. The proportion must be greater than or equal to zero and less than one. Enter zero here for no loss to follow-up.

Sample Size (When Not Solving for Sample Size)

Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal (N1 = N2)**
This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.
- **Enter N1 and N2 individually**
This choice permits you to enter different values for $N1$ and $N2$.
- **Enter N1 and R, where N2 = R * N1**
Choose this option to specify a value (or values) for $N1$, and obtain $N2$ as a ratio (multiple) of $N1$.
- **Enter total sample size and percentage in Group 1**
Choose this option to specify a value (or values) for the total sample size (N), obtain $N1$ as a percentage of N , and then $N2$ as $N - N1$.

Sample Size Per Group

This option is displayed only if Group Allocation = "Equal (N1 = N2)."

The Sample Size Per Group is the number of items or individuals sampled from each of the Group 1 and Group 2 populations. Since the sample sizes are the same in each group, this value is the value for $N1$, and also the value for $N2$.

The Sample Size Per Group must be ≥ 2 . You can enter a single value or a series of values.

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N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = “Enter N1 and N2 individually” or “Enter N1 and R, where $N2 = R * N1$.”*

$N1$ is the number of items or individuals sampled from the Group 1 population.

$N1$ must be ≥ 2 . You can enter a single value or a series of values.

N2 (Sample Size, Group 2)

This option is displayed only if Group Allocation = “Enter N1 and N2 individually.”

$N2$ is the number of items or individuals sampled from the Group 2 population.

$N2$ must be ≥ 2 . You can enter a single value or a series of values.

R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = “Enter N1 and R, where $N2 = R * N1$.”*

R is the ratio of $N2$ to $N1$. That is,

$$R = N2/N1$$

Use this value to obtain $N2$ as a multiple (or proportion) of $N1$.

$N2$ is calculated from $N1$ using the formula:

$$N2 = [R \times N1],$$

where the value $[Y]$ is the next integer $\geq Y$.

For example, setting $R = 2.0$ results in a Group 2 sample size that is double the sample size in Group 1.

R must be greater than 0. If $R < 1$, then $N2$ will be less than $N1$; if $R > 1$, then $N2$ will be greater than $N1$. You can enter a single value or a series of values.

Total Sample Size (N)

This option is displayed only if Group Allocation = “Enter total sample size and percentage in Group 1.”

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines $N1$ and $N2$.

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 2.

You can enter a single value or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = “Enter total sample size and percentage in Group 1.”

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

p1 (Proportion of N in Control Group)

This is the proportion of N in the control group. If this value were labeled p_1 , the sample size of the control group is Np_1 and the sample size of treatment group is $N - Np_1$. Note that the value of Np_1 is rounded to the nearest integer. The proportion must be between zero and one. Enter 0.5 for equal sample sizes in both groups.

You may enter a single value such as 0.5 or a range of values such as 0.4 0.5 0.6 or 0.4 to 0.6 by 0.1.

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W (Proportion Lost to Follow-Up)

This is the proportion of subjects that are lost to follow-up. The sample size is adjusted to account for this loss using the formula

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

where W is the proportion lost to follow-up. The proportion must be greater than or equal to zero and less than one. Enter zero here for no loss to follow-up.

Sample Size – Duration

R (Accrual Time)

The length of time during which patients can enter the study. The value must be greater than zero and should be specified in the same units of time measurement as the fixed time point T_0 and the follow-up time.

You may enter a single value such as 5 or a range of values such as 4 5 6 or 4 to 6 by 1.

T–R (Follow-Up Time)

The length of time between the entry of the last individual (R) and the end of the study (T). Hence, the follow-up time is equal to $T - R$. The value must be greater than zero and should be specified in the same units of time measurement as the fixed time point T_0 and the accrual time.

You may enter a single value such as 5 or a range of values such as 4 5 6 or 4 to 6 by 1.

Hazard Ratio

Specify the Hazard Ratio Using

Use this option to choose what information you will enter to specify the hazard ratio. You can enter a hazard ratio directly, along with the control group incidence or survival proportions. You can also enter incidence values or survival proportions for both the treatment and control groups, in which case PASS will compute the hazard ratio for you.

If you enter a hazard ratio directly, then the assumption is required that the hazard rates for competing risks are equal in the two groups, i.e. $h_{cr,1} = h_{cr,2}$.

Cumulative Incidence

A cumulative incidence value represents the proportion of individuals that fail before the time point, T_0 .

Survival Proportion

A survival proportion represents the proportion of individuals that survive past the time point, T_0 .

Options

The following four options are available:

- **Cumulative Incidences**

Choose this option if you want to enter cumulative incidence values for both the control and treatment groups.

- **Control Cumulative Incidences and Hazard Ratio**

Choose this option if you have cumulative incidence values for the event of interest and competing risks in the control group only, but have a hazard ratio to enter.

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This option requires the assumption that the hazard rates for competing risks are equal in the two groups, i.e. $h_{cr,1} = h_{cr,2}$.

- **Survival Proportions**

Choose this option if you want to enter survival proportions for both the control and treatment groups.

- **Control Survival Proportions and Hazard Ratio**

Choose this option if you have survival proportions for the event of interest and competing risks in the control group only, but have a hazard ratio to enter.

This option requires the assumption that the hazard rates for competing risks are equal in the two groups, i.e. $h_{cr,1} = h_{cr,2}$.

Note

When there are no competing risk factors, then Cumulative Incidence = 1 – Survival Proportion. In the presence of competing risks, this equality does not hold.

T0 (Fixed Time Point)

This is an arbitrary time value used to convert survival proportions and cumulative incidences into hazard rates. When you talk about incidence or survival, you must include a time period over which the incidence or survival occurred. That is, you must say 40% incidence or 50% survival in, say, five years. This value is the time period.

For example, a value of 3 here and cumulative incidence = 0.4 means that you observe 40% incidence in 3 years.

T_0 must be greater than zero. This value should be specified in the same units of time measurement as the accrual time and the follow-up time.

Hazard Ratio – Event of Interest

Fev1(T0) and Fev2(T0) (Event of Interest – Cumulative Incidences at Time T0)

Enter the cumulative incidence at time T_0 (i.e. the proportion of individuals that fail before time T_0) for the main event of interest in this group. For example, in a study of cancer survival, the main event of interest would be death attributable directly to cancer. There are, however, many other causes that may result in a patient's death such as accidents, heart disease, or diabetes. These other causes are called the competing risks.

$F_{ev,i}(T_0)$ must be between 0 and $1 - F_{cr,i}(T_0)$. That is, $F_{ev,i}(T_0) + F_{cr,i}(T_0) < 1$.

You may enter a single value such as 0.5 or a range of values such as 0.4 0.5 0.6 or 0.4 to 0.6 by 0.1.

Sev1(T0) and Sev2(T0) (Event of Interest – Survival Proportions at Time T0)

Enter the survival proportion at time T_0 (i.e. the proportion of individuals that survive past time T_0) for the main event of interest in this group. This proportion is usually estimated from a Kaplan-Meier curve. For example, in a study of cancer survival, the main event of interest would be death attributable directly to cancer. There are, however, many other causes that may result in a patient's death such as accidents, heart disease, or diabetes. These other causes are called the competing risks.

$S_{ev,i}(T_0)$ must be between zero and one, with $S_{ev,1}(T_0) \neq S_{ev,2}(T_0)$.

You may enter a single value such as 0.5 or a range of values such as 0.4 0.5 0.6 or 0.4 to 0.6 by 0.1.

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HR (Hazard Ratio = $h_{ev,2}/h_{ev,1}$)

Enter a value for the hazard ratio to detect for the event of interest. The hazard ratio is calculated as

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

the hazard rate of the treatment group divided by the hazard rate of the control group. This value must be greater than zero but not equal to one.

You may enter a single value such as *0.5* or a range of values such as *0.4 0.5 0.6* or *0.4 to 0.6 by 0.1*.

Hazard Ratio – Competing Risks

Fcr1(T0) and Fcr2(T0) (Competing Risks – Cumulative Incidences at Time T0)

Enter the cumulative incidence at time $T0$ (i.e. the proportion of individuals that fail before time $T0$) for competing risks in this group. For example, in a study of cancer survival, the main event of interest would be death attributable directly to cancer. There are, however, many other causes that may result in a patient's death such as accidents, heart disease, or diabetes. These other causes are called the competing risks.

$F_{cr,i}(T0)$ must be between 0 and $1 - F_{ev,i}(T0)$. That is, $F_{ev,i}(T0) + F_{cr,i}(T0) < 1$.

You may enter a single value such as *0.5* or a range of values such as *0.4 0.5 0.6* or *0.4 to 0.6 by 0.1*.

Scr1(T0) and Scr2(T0) (Event of Interest – Survival Proportions at Time T0)

Enter the survival proportion at time $T0$ (i.e. the proportion of individuals that survive to time $T0$) for competing risks in this group. This proportion is usually estimated from a Kaplan-Meier curve. For example, in a study of cancer survival, the main event of interest would be death attributable directly to cancer. There are, however, many other causes that may result in a patient's death such as accidents, heart disease, or diabetes. These other causes are called the competing risks.

$S_{cr,i}(T0)$ must be between zero and one.

You may enter a single value such as *0.5* or a range of values such as *0.4 0.5 0.6* or *0.4 to 0.6 by 0.1*.

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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. 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
Group Allocation	Enter total sample size and percentage in Group 1
Total Sample Size (N)	100 to 900 by 100
Percent in Group 1	50
W (Proportion Lost to Follow-Up)	0.1
R (Accrual Time)	4
T-R (Follow-Up Time)	3
Specify the Hazard Ratio Using	Cumulative Incidences
T0 (Fixed Time Point)	3
Fev1(T0) (Control)	0.10
Fev2(T0) (Treatment)	0.05
Fcr1(T0) (Control)	0.65
Fcr2(T0) (Treatment)	0.65

Logrank Tests Accounting for Competing Risks

Annotated Output

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

Numeric Results

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.1

		Ctrl	Trt	Prop	Hazard	Ctrl	Trt	Ctrl	Trt	Follow			
Power	N	N1	N2	Ctrl	Ratio	Main	Main	Comp	Comp	Accr'l	Up	Alpha	Rpt
				p1	HR	Event	Event	Risks	Risks	Time	Time		Row
						Incid	Incid	Incid	Incid	R	T-R		
						Fev1	Fev2	Fcr1	Fcr2				
0.19094	100	50	50	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	1
0.33549	200	100	100	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	2
0.46820	300	150	150	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	3
0.58358	400	200	200	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	4
0.67986	500	250	250	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	5
0.75772	600	300	300	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	6
0.81912	700	350	350	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	7
0.86657	800	400	400	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	8
0.90261	900	450	450	0.5	0.4653	0.1000	0.0500	0.6500	0.6500	4	3	0.050	9

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.1 (Continued)

		Ctrl	Trt	Total	Ctrl	Trt	Ctrl	Trt	Ctrl	Trt	Ctrl	Trt	
Beta	E	E1	E2	Prob	Prob	Prob	Event	Event	Hazard	Hazard	Hazard	Hazard	Rpt
				Event	Event	Event	Rate	Rate	Rate	Rate	Rate	Rate	Row
				Pr(ev)	Pr(ev1)	Pr(ev2)	hev1	hev2	hcr1	hcr2			
0.80906	8.1	5.3	2.7	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			1
0.66451	16.1	10.6	5.5	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			2
0.53180	24.2	15.9	8.2	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			3
0.41642	32.2	21.3	10.9	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			4
0.32014	40.3	26.6	13.7	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			5
0.24228	48.3	31.9	16.4	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			6
0.18088	56.4	37.2	19.1	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			7
0.13343	64.4	42.5	21.9	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			8
0.09739	72.5	47.8	24.6	0.0895	0.1181	0.0608	0.0616	0.0287	0.4005	0.3727			9

References

- 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.

Report Definitions

- T0 is the base time at which the cumulative incidences are calculated.
- W is the proportion of the individuals lost to follow-up during the entire study.
- Power is the probability of rejecting a false null hypothesis. Power should be close to one.
- N is the total sample size of both groups combined.
- N1 and N2 are the sample sizes for the control and treatment groups, respectively.
- p1 is the proportion of the total sample size (N) that is assigned to the control group.
- HR is 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 are the cumulative incidences at time T0 for the event of interest in the control and treatment groups, respectively.
- Fcr1 and Fcr2 are the cumulative incidences at time T0 for the competing risk factors in the control and treatment groups, respectively.
- R is the accrual or entry time for the study.
- T-R is the follow-up time for the study. T is the total time.
- Alpha is the probability of rejecting a true null hypothesis. It should be small.
- Beta is the probability of accepting a false null hypothesis. It should be small.
- E is the total number of events required for the study.
- E1 and E2 are the number of events required for the control and treatment groups, respectively.
- Pr(ev) is the overall probability of observing the event of interest during the study.
- Pr(ev1) and Pr(ev2) are the probability of observing the event of interest in a subject during the study for the control and treatment groups, respectively.
- hev1 and hev2 are the hazard rates for the event of interest in the control and treatment groups, respectively.
- hcr1 and hcr2 are the hazard rates for the competing risk factors in the control and treatment groups, respectively.
- Rpt Row is a line number assigned to allow corresponding report lines to be identified.

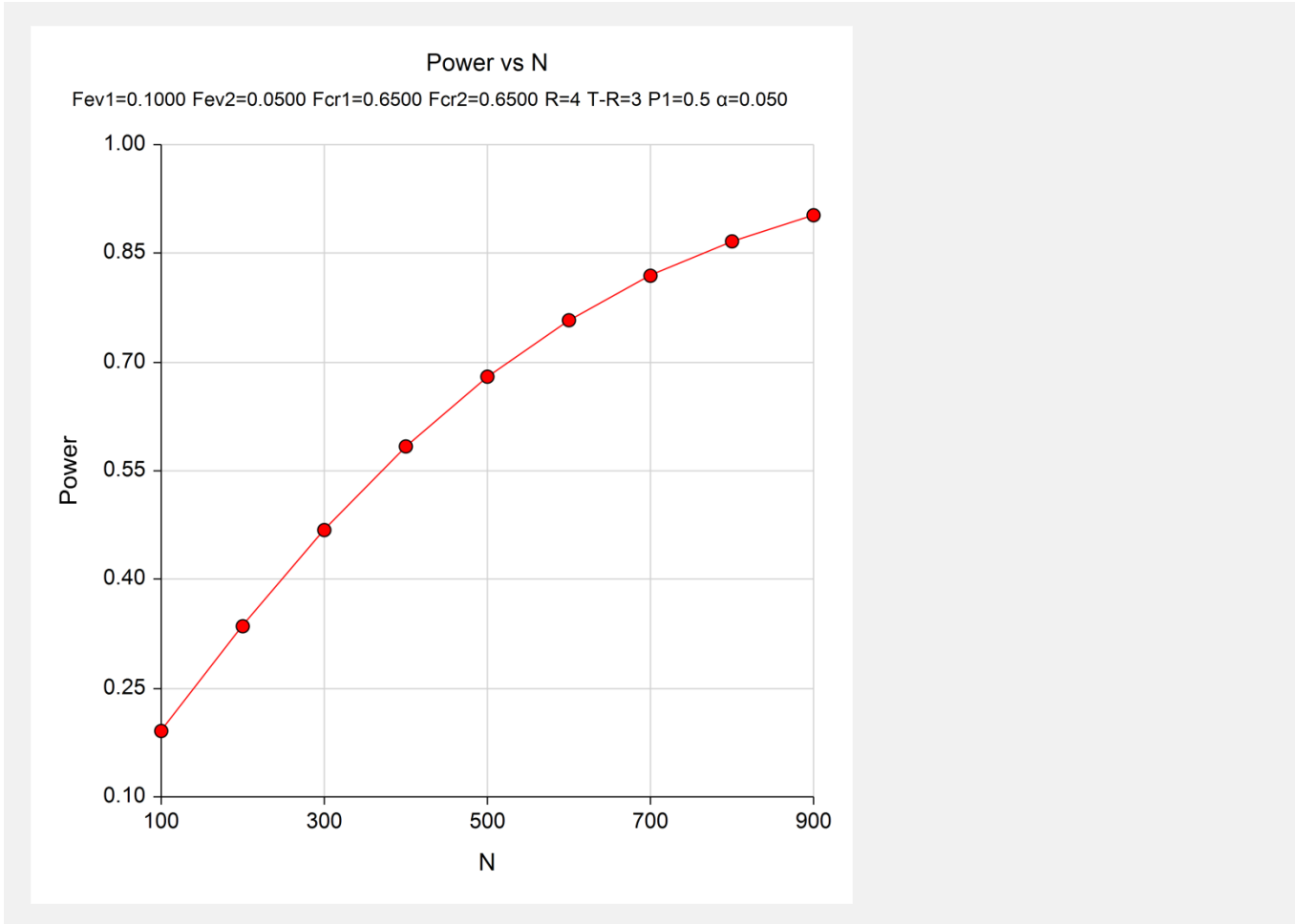
Logrank Tests Accounting for Competing Risks

Summary Statements

When accounting for competing risks, a two-sided logrank test with an overall sample size of 100 subjects (50 in the control group and 50 in the treatment group) achieves 19.094% power at a 0.050 significance level to detect a hazard ratio of 0.4653. The study lasts for 7 time periods with an accrual (entry) time of 4 periods and a follow-up time of 3 periods. The cumulative incidence proportions at time 3 for the event of interest are 0.1000 in the control group and 0.0500 in the treatment group. The cumulative incidence proportions at time 3 for the competing risk factors are 0.6500 in the control group and 0.6500 in the treatment group. The proportion of subjects lost to follow-up during the entire study is 0.1.

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



This plot shows the relationship between power and sample size.

Logrank Tests Accounting for Competing Risks

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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. 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	Sample Size
Alternative Hypothesis	Two-Sided
Power	0.90
Alpha	0.05
Group Allocation	Equal (N1 = N2)
W (Proportion Lost to Follow-Up)	0.1
R (Accrual Time)	4
T-R (Follow-Up Time)	2 3 5
Specify the Hazard Ratio Using	Control Cumulative Incidences and Hazard Ratio
T0 (Fixed Time Point)	3
Fev1(T0) (Control)	0.10
HR (Hazard Ratio = hev2 / hev1)	0.4 to 0.8 by 0.1
Fcr1(T0) (Control)	0.65

Output

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

Numeric Results

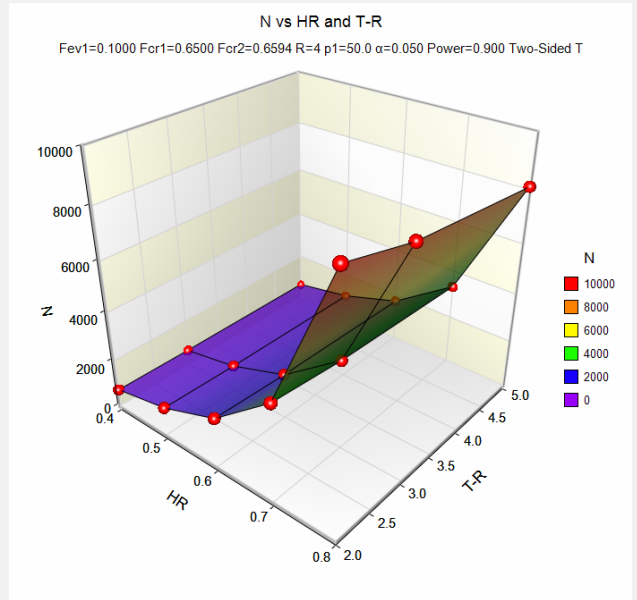
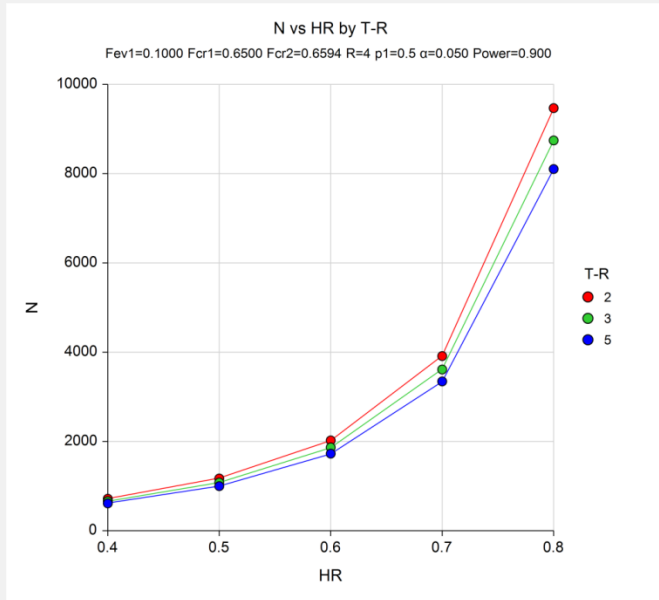
Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.1

Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Incid Fev1	Trt Main Event Incid Fev2	Ctrl Comp Risks Incid Fcr1	Trt Comp Risks Incid Fcr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.90010	717	358	359	0.5	0.4000	0.1000	0.0418	0.6500	0.6789	4	2	0.050	1
0.90010	662	331	331	0.5	0.4000	0.1000	0.0418	0.6500	0.6789	4	3	0.050	2
0.90038	613	306	307	0.5	0.4000	0.1000	0.0418	0.6500	0.6789	4	5	0.050	3
0.90022	1170	585	585	0.5	0.5000	0.1000	0.0518	0.6500	0.6740	4	2	0.050	4
0.90008	1079	539	540	0.5	0.5000	0.1000	0.0518	0.6500	0.6740	4	3	0.050	5
0.90026	999	499	500	0.5	0.5000	0.1000	0.0518	0.6500	0.6740	4	5	0.050	6
0.90014	2023	1011	1012	0.5	0.6000	0.1000	0.0618	0.6500	0.6691	4	2	0.050	7
0.90006	1866	933	933	0.5	0.6000	0.1000	0.0618	0.6500	0.6691	4	3	0.050	8
0.90005	1727	863	864	0.5	0.6000	0.1000	0.0618	0.6500	0.6691	4	5	0.050	9
0.90006	3913	1956	1957	0.5	0.7000	0.1000	0.0715	0.6500	0.6642	4	2	0.050	10
0.90004	3612	1806	1806	0.5	0.7000	0.1000	0.0715	0.6500	0.6642	4	3	0.050	11
0.90007	3345	1672	1673	0.5	0.7000	0.1000	0.0715	0.6500	0.6642	4	5	0.050	12
0.90001	9468	4734	4734	0.5	0.8000	0.1000	0.0812	0.6500	0.6594	4	2	0.050	13
0.90001	8744	4372	4372	0.5	0.8000	0.1000	0.0812	0.6500	0.6594	4	3	0.050	14
0.90002	8103	4051	4052	0.5	0.8000	0.1000	0.0812	0.6500	0.6594	4	5	0.050	15

Logrank Tests Accounting for Competing Risks

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.1 (Continued)

Beta	E	Ctrl E1	Trt E2	Total Prob Event Pr(ev)	Ctrl Prob Event Pr(ev1)	Trt Prob Event Pr(ev2)	Ctrl Event Hazard Rate hev1	Trt Event Hazard Rate hev2	Ctrl Comp Risks Hazard Rate hcr1	Trt Comp Risks Hazard Rate hcr2	Rpt Row
0.09990	50.1	35.2	14.9	0.0776	0.1092	0.0461	0.0616	0.0246	0.4005	0.4005	1
0.09990	50.1	35.1	14.9	0.0842	0.1181	0.0502	0.0616	0.0246	0.4005	0.4005	2
0.09962	50.1	35.1	15.1	0.0910	0.1273	0.0546	0.0616	0.0246	0.4005	0.4005	3
0.09978	87.5	57.5	30.0	0.0831	0.1092	0.0571	0.0616	0.0308	0.4005	0.4005	4
0.09992	87.5	57.4	30.1	0.0901	0.1181	0.0621	0.0616	0.0308	0.4005	0.4005	5
0.09974	87.6	57.2	30.3	0.0974	0.1273	0.0675	0.0616	0.0308	0.4005	0.4005	6
0.09986	161.1	99.4	61.8	0.0885	0.1092	0.0679	0.0616	0.0370	0.4005	0.4005	7
0.09994	161.1	99.2	61.9	0.0960	0.1181	0.0738	0.0616	0.0370	0.4005	0.4005	8
0.09995	161.1	98.9	62.2	0.1037	0.1273	0.0800	0.0616	0.0370	0.4005	0.4005	9
0.09994	330.4	192.3	138.2	0.0939	0.1092	0.0785	0.0616	0.0431	0.4005	0.4005	10
0.09996	330.4	192.0	138.4	0.1017	0.1181	0.0852	0.0616	0.0431	0.4005	0.4005	11
0.09993	330.5	191.6	138.9	0.1098	0.1273	0.0923	0.0616	0.0431	0.4005	0.4005	12
0.09999	844.1	465.3	378.8	0.0991	0.1092	0.0889	0.0616	0.0493	0.4005	0.4005	13
0.09999	844.1	464.8	379.3	0.1073	0.1181	0.0964	0.0616	0.0493	0.4005	0.4005	14
0.09998	844.2	464.1	380.0	0.1158	0.1273	0.1042	0.0616	0.0493	0.4005	0.4005	15



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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. You may then make the appropriate entries as listed below or open **Example 3a** 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
Group Allocation	Enter total sample size and percentage in Group 1
Total Sample Size (N).....	150
Percent in Group 1.....	50
W (Proportion Lost to Follow-Up)	0
R (Accrual Time).....	3
T-R (Follow-Up Time)	2
Specify the Hazard Ratio Using.....	Control Survival Proportions and Hazard Ratio
T0 (Fixed Time Point)	3
Sev1(T0) (Control).....	0.5
HR (Hazard Ratio = $hev2 / hev1$)	0.5
Scr1(T0) (Control).....	0.4
Reports Tab	
Power and Beta Decimals	7

Logrank Tests Accounting for Competing Risks

Output

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

Numeric Results

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.0													
Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Surv Sev1	Trt Main Event Surv Sev2	Ctrl Comp Risks Surv Scr1	Trt Comp Risks Surv Scr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.6162274	150	75	75	0.5	0.5000	0.5000	0.7071	0.4000	0.4000	3	2	0.050	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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. You may then make the appropriate entries as listed below or open **Example 3b** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	Power
Alternative Hypothesis	Two-Sided
Alpha.....	0.05
Group Allocation	Enter total sample size and percentage in Group 1
Total Sample Size (N).....	150
Percent in Group 1.....	50
W (Proportion Lost to Follow-Up)	0
R (Accrual Time).....	3
T-R (Follow-Up Time)	2
Specify the Hazard Ratio Using.....	Control Cumulative Incidences and Hazard Ratio
T0 (Fixed Time Point)	3
Fev1(T0) (Control)	0.345
HR (Hazard Ratio = hev2 / hev1)	0.5
Fcr1(T0) (Control)	0.455
Reports Tab	
Power and Beta Decimals	7

Logrank Tests Accounting for Competing Risks

Output

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

Numeric Results

Numeric Results for a Two-Sided Test with $T_0 = 3$ and $W = 0.0$

Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Incid Fev1	Trt Main Event Incid Fev2	Ctrl Comp Risks Incid Fcr1	Trt Comp Risks Incid Fcr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.6168332	150	75	75	0.5	0.5000	0.3450	0.1971	0.4550	0.5199	3	2	0.050	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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. You may then make the appropriate entries as listed below or open **Example 3c** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	Power
Alternative Hypothesis	Two-Sided
Alpha.....	0.05
Group Allocation	Enter total sample size and percentage in Group 1
Total Sample Size (N).....	150
Percent in Group 1.....	50
W (Proportion Lost to Follow-Up)	0
R (Accrual Time).....	3
T-R (Follow-Up Time)	2
Specify the Hazard Ratio Using.....	Survival Proportions
T0 (Fixed Time Point)	3
Sev1(T0) (Control).....	0.5
Sev2(T0) (Treatment)	0.706
Scr1(T0) (Control).....	0.4
Scr2(T0) (Treatment).....	0.3
Reports Tab	
Power and Beta Decimals	7

Logrank Tests Accounting for Competing Risks

Output

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

Numeric Results

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.0													
Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Surv Sev1	Trt Main Event Surv Sev2	Ctrl Comp Risks Surv Scr1	Trt Comp Risks Surv Scr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.5924636	150	75	75	0.5	0.5023	0.5000	0.7060	0.4000	0.3000	3	2	0.050	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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. You may then make the appropriate entries as listed below or open **Example 3d** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	Power
Alternative Hypothesis	Two-Sided
Alpha.....	0.05
Group Allocation	Enter total sample size and percentage in Group 1
Total Sample Size (N).....	150
Percent in Group 1.....	50
W (Proportion Lost to Follow-Up)	0
R (Accrual Time).....	3
T-R (Follow-Up Time)	2
Specify the Hazard Ratio Using.....	Cumulative Incidences
T0 (Fixed Time Point)	3
Fev1(T0) (Control)	0.345
Fev2(T0) (Treatment)	0.177
Fcr1(T0) (Control)	0.455
Fcr2(T0) (Treatment)	0.61

Reports Tab

Logrank Tests Accounting for Competing Risks

Power and Beta Decimals 7

Output

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

Numeric Results

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.0													
Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Incid Fev1	Trt Main Event Incid Fev2	Ctrl Comp Risks Incid Fcr1	Trt Comp Risks Incid Fcr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.5958667	150	75	75	0.5	0.5011	0.3450	0.1770	0.4550	0.6100	3	2	0.050	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

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. You may then make the appropriate entries as listed below or open **Example 3e** 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
Group Allocation	Enter total sample size and percentage in Group 1
Total Sample Size (N)	150
Percent in Group 1	50
W (Proportion Lost to Follow-Up)	0
R (Accrual Time)	3
T-R (Follow-Up Time)	2
Specify the Hazard Ratio Using	Survival Proportions
T0 (Fixed Time Point)	3

Logrank Tests Accounting for Competing Risks

Design Tab (Continued)

Sev1(T0) (Control)	0.5
Sev2(T0) (Treatment)	0.706
Scr1(T0) (Control)	1
Scr2(T0) (Treatment)	1

Reports Tab

Power and Beta Decimals	7
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Output

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

Numeric Results

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.0													
Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Surv Sev1	Trt Main Event Surv Sev2	Ctrl Comp Risks Surv Scr1	Trt Comp Risks Surv Scr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.7969974	150	75	75	0.5	0.5023	0.5000	0.7060	1.0000	1.0000	3	2	0.050	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)

Logrank Tests Accounting for Competing Risks

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 Accounting for Competing Risks** procedure window by expanding **Survival**, then **Two Survival Curves**, then clicking **Competing Risks**, and then clicking on **Logrank Tests Accounting for Competing Risks**. You may then make the appropriate entries as listed below or open **Example 4a** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Alternative Hypothesis	Two-Sided
Power.....	0.80
Alpha.....	0.05
Group Allocation	Equal (N1 = N2)
W (Proportion Lost to Follow-Up)	0
R (Accrual Time).....	9
T-R (Follow-Up Time)	10
Specify the Hazard Ratio Using.....	Cumulative Incidences
T0 (Fixed Time Point)	10
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

Numeric Results for a Two-Sided Test with T0 = 10 and W = 0.0													
		Ctrl	Trt	Prop	Hazard	Ctrl	Trt	Ctrl	Trt		Follow		Rpt
Power	N	N1	N2	Ctrl	Ratio	Main	Main	Comp	Comp	Accr'l	Up	Alpha	Row
				p1	HR	Event	Event	Risks	Risks	Time	Time		
						Incid	Incid	Incid	Incid	R	T-R		
0.80009	2355	1177	1178	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	1
Numeric Results for a Two-Sided Test with T0 = 10 and W = 0.0 (Continued)													
		Ctrl	Trt	Total	Ctrl	Trt	Ctrl	Trt	Ctrl	Trt	Ctrl	Trt	Rpt
Beta	E	E1	E2	Prob	Prob	Prob	Event	Event	Hazard	Hazard	Hazard	Hazard	Row
				Pr(ev)	Pr(ev1)	Pr(ev2)	Rate	Rate	Rate	Rate	Rate	Rate	
					hev1	hev2	hev1	hev2	hcr1	hcr2	hcr1	hcr2	

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.

Logrank Tests Accounting for Competing Risks

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.

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

Numeric Results for a Two-Sided Test with T0 = 10 and W = 0.0													
Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Incid Fev1	Trt Main Event Incid Fev2	Ctrl Comp Risks Incid Fcr1	Trt Comp Risks Incid Fcr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.79993	2354	1177	1177	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	1
0.80009	2355	1177	1178	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	2
0.80026	2356	1178	1178	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	3
0.80192	2366	1183	1183	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	4
0.80208	2367	1183	1184	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	5
0.80225	2368	1184	1184	0.5	2.04089	0.01500	0.03000	0.68000	0.68000	9	10	0.050	6

Numeric Results for a Two-Sided Test with T0 = 10 and W = 0.0 (Continued)													
Beta	E	Ctrl E1	Trt E2	Total Prob Event Pr(ev)	Ctrl Prob Event Pr(ev1)	Trt Prob Event Pr(ev2)	Ctrl Event Hazard Rate hev1	Trt Event Hazard Rate hev2	Ctrl Comp Risks Hazard Rate hcr1	Trt Comp Risks Hazard Rate hcr2	Rpt Row		
0.20007	61.68	20.64	41.04	0.02620	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	1		
0.19991	61.71	20.65	41.05	0.02620	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	2		
0.19974	61.73	20.66	41.07	0.02620	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	3		
0.19808	61.99	20.75	41.24	0.02620	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	4		
0.19792	62.02	20.76	41.26	0.02620	0.01754	0.03486	0.00256	0.00523	0.11618	0.11856	5		
0.19775	62.05	20.77	41.28	0.02620	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.