



## Comparing Survival Curves (time-to-event data)

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## 1 Motivation

In many animal experimentation studies, the main outcome/endpoint variable is the time to the occurrence of a particular event. In a randomized controlled trial of certain disease, for example, two or more drugs might be compared with respect to time from randomization and the start of therapy until surrogate death. Here the event is surrogate death. Other examples of an event are time to tumor recurrence and time to cardiovascular surrogate death.

Such observations are generally referred to by the generic term *survival data* or equivalently *time-to-event data* even when the endpoint or event being considered is not death but something else. Such data generally require special techniques for analysis for two main reasons:

- Survival data are inherently positive and generally not symmetrically distributed – they will often appear positively skewed, with a few subjects surviving a very long time compared with the majority; so assuming a normal distribution will not be reasonable.
- At the completion of the study, some subjects may not have reached the endpoint of interest (surrogate death, relapse, etc.). Consequently, the exact survival times are greater than the amount of time the subject has been in the study. The survival times of these subjects are said to be *censored* (precisely, they are right-censored).

Why cannot we use linear regression to model the survival time as a function of a set of predictor variables? It is because (i) the time to event is restricted to be positive, which has a skewed distribution, (ii) the interest is to model probability of surviving past a certain point in time and (iii) it cannot effectively handle the censoring of the observations.

Why cannot we use logistic regression to model the dichotomous event outcome (ie, to model the probability of having an event)? It is because the same last two reasons above as in the linear regression and because it will have lower power since it only considers whether each subject had the event, not the time until the subject possibly had the event (also, it inherently assumes that the time until the event is the same for all subjects).

## 2 Basic terminology

Of central importance in the analysis of time-to-event data are two functions used equivalently to describe their distribution, namely the *survival function* and the *hazard function*.

Throughout this note, let  $T > 0$  denote the random variable representing the time to the occurrence of a particular event. We consider  $T$  a continuous random variable. Its probability density function (pdf) is denoted by  $f(t)$  and its cumulative distribution function (cdf) is denoted by  $F(t)$ .

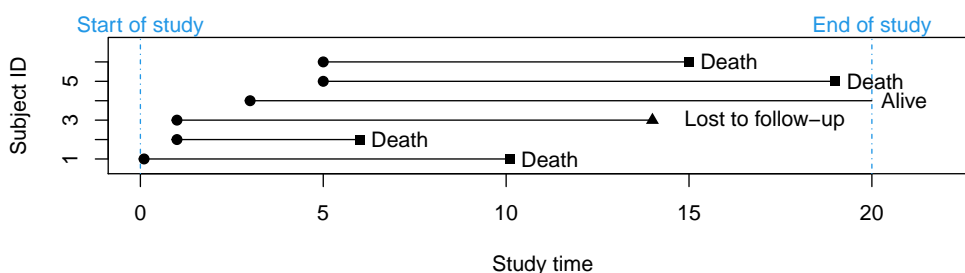
### 2.1 Censoring

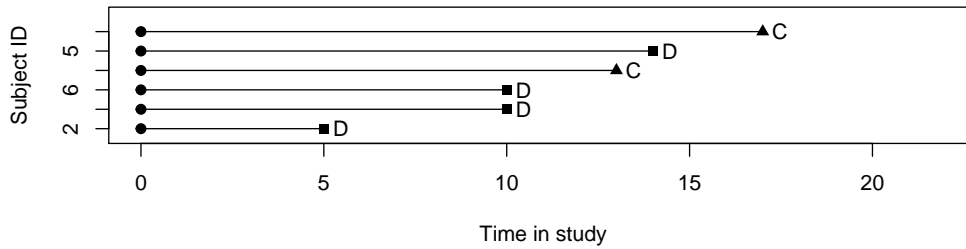
The main characteristic of most survival data is censoring. That is when the value of an observation is only partially known. A typical study is designed to recruit subjects within a certain time frame and to follow them until the end of the study. In many cases, the end of the study occurs before every individual in the data set has died or experienced the event of interest. Those individuals that are still alive and observed at the end of the observation time are called censored. Sometimes subjects die from a cause other than the trial endpoint or from other reasons unrelated to the endpoint of interest, both denoted as *lost to follow-up*, and are considered another instance of censoring. All of these situations are called "right censoring".

Thus, right censoring is when the time to the event is known to be greater than some value. Other types of censoring are: (i) left censoring (the time to the event is known to be less than some value), (ii) interval censoring (the time to the event is known to be in a specified interval), (iii) type I censoring (stop the trial after a predetermined time, eg, at 2 years follow-up) and (iv) type II censoring (stop the trial after a predetermined number of events have occurred). The most common censoring mechanism in survival data is the right censoring. Therefore we focus on this type of censoring.

Here and in many practical applications we assume that the censoring is independent (non-informative) of what would cause a subject to have an event. If this is not the case, informative censoring is said to be present. For example, if a subject is pulled off of a drug because of a treatment failure, the censoring time is indirectly reflecting a bad clinical outcome (resulting analysis will be biased).

The figure below shows example survival data for six individuals. Four individuals have died while under observation, indicated by black squares at their observed times of death (Subjects 1, 2, 5 and 6). Subject 3 was lost to follow-up and Subject 4 was still alive at last observation.





The top panel shows the individual during the study time. Lower panel shows the absolute survival times, D: death, C: censoring. The age of the individuals (or other covariates) are not indicated in the plot.

Further details on the topic can be found at [Furrer, Reinhard and the Applied Statistics Group \(2020\)](#), a lecture note on Statistical Modeling.

## 2.2 Survival function

The survival function of  $T$  is denoted by  $S(t)$  and is defined as the probability of surviving beyond any specified time point  $t$ . Mathematically this is written as

$$S(t) := P(T > t) .$$

Using the cdf of  $T$ , the definition above is equivalent to  $S(t) = 1 - F(t)$ . The function is non-increasing over time  $t$  with  $S(0) = 1$  and  $\lim_{t \rightarrow \infty} S(t) = 0$ . In theory, the survival function is smooth. In practice, we observe events on discrete time scale (days, weeks, months, etc.). For example, time to tumor recurrence (in days) or time to cardiovascular surrogate death (in weeks).

## 2.3 Hazard function

The hazard function of  $T$  is denoted by  $h(t)$  and is defined as the probability that a subject experiences the event in a very small time interval,  $\Delta$ , given that the subject has survived up to the beginning of the interval. Mathematically, this is written as

$$h(t) := \lim_{\Delta \rightarrow 0} \frac{P(t \leq T \leq t + \Delta \mid T \geq t)}{\Delta} .$$

That is, the instantaneous rate at which events occur, given no previous event. The conditioning feature of this definition is very important. For example, the probability of dying at age 100 is very small because most people die before that age. In contrast, the probability of a person dying just after age 100 who has reached that age is of much greater. Note that a hazard function can be: constant over time, or decreasing over time, or increasing over time, or anything else as well.

The survival function and the hazard function are related by the formula  $h(t) = f(t)/S(t)$  .

## 2.4 Example: Exponential distribution family

A simple parametric/theoretical distribution for time-to-event random variable is an **exponential distribution**. This distribution has only one parameter, typically denoted by  $\lambda$ . This parameter is called rate parameter and it takes only a positive real value. Mathematically we write  $T \sim \text{Exp}(\lambda)$ . The **mean** and the **variance** of

this random variable is  $1/\lambda$  and  $1/\lambda^2$ , respectively. The cdf of  $T$  is given by  $F(t) = 1 - \exp(-\lambda t)$ . The pdf of  $T$  is  $f(t) = \lambda \exp(-\lambda t)$ , which is simply the derivative of the cdf. The survival function and the hazard function of an exponential time-to-event are respectively given as

$$S(t) = 1 - F(t) = \exp(-\lambda t) ,$$

$$h(t) = \frac{f(t)}{S(t)} = \frac{\lambda \exp(-\lambda t)}{\exp(-\lambda t)} = \lambda .$$

Under assumption of exponential distribution of time-to-event, the **hazard function is constant over time** with value of  $\lambda$ . This property is called "lack-of memory". By solving  $S(t) = \exp(-\lambda t) = 1/2$  for  $t$ , we get the **median** survival time  $\ln(2)/\lambda$ .

Exponential distributions are one of the common assumption taken in survival models, because it is the **simplest** distribution that can be used to characterized survival data and it is **easy to interpret**. Other families of distribution are 2-parameter Gamma distribution, Weibull distribution, log-normal distribution. The exponential distribution is a special case of 2-parameter Gamma distribution as well as of Weibull distribution.

### 3 Estimating survival function

An estimate of survival function  $S(t)$  is denoted by  $\hat{S}(t)$ . When there are no censored observations in the sample of survival times, a non-parametric survivor function can be estimated simple as

$$\hat{S}(t) = \frac{\text{number of subjects with survival times } \geq t}{n}$$

where  $n$  is the total number of subjects/observations. This simple estimate cannot be used for survival times when censored observations are present.

#### 3.1 Non-parametric estimate (Kaplan Meier)

When censored times are present, the survival function is estimated using the **Kaplan-Meier (KM)** estimate. We first order the survival times from the smallest to the largest such that  $\tau_1 \leq \tau_2 \leq \dots \leq \tau_j$ , where  $\tau_j$  is the  $j$ th largest unique survival time. The KM estimate is

$$\hat{S}(t) = \prod_{j: \tau_j \leq t} \left(1 - \frac{d_j}{r_j}\right)$$

where  $d_j$  is the number of subjects who experience the event at time  $\tau_j$  and  $r_j$  is the number of subjects at risk prior to  $\tau_j$  (including those censored at  $\tau_j$ ).

The idea of KM estimate is to use the law of conditional probability:

$$\begin{aligned} S(t) = P(T > t) &= \prod_{j: \tau_j \leq t} P(\text{survive at time } \tau_j \mid \text{at risk at } \tau_{j-1}) \\ &= \prod_{j: \tau_j \leq t} (1 - P(\text{die at time } \tau_j \mid \text{at risk at } \tau_{j-1})) \\ &= \prod_{j: \tau_j \leq t} \left(1 - \frac{d_j}{r_j}\right) . \end{aligned}$$

Therefore, KM estimate is called *product limit* estimate, a name given by Kaplan and Meier in 1958.

## 3.2 Logrank test

In comparing survival curves (for example, two treatment groups of a control and an intervention), the logrank test is mostly used. The test is nonparametric and is easy to apply. The assumptions are: (i) the subjects in the two groups are homogeneous in all aspects except the treatment (identical property), (ii) the allocation of the treatment is based on randomization and not on characteristics of subjects (independent property), and (iii) survival function of each group follows exponential distribution (i.e., constant hazard rate for each group).

Generally, suppose there are  $k+1$  treatment groups, denoted by  $0, 1, \dots, k$  and we wish to test the null hypothesis

$$H_0 : S_0(t) = S_1(t) = \dots = S_k(t)$$

where group 0 is a control group and group  $i$  is an intervention  $i$  with  $i = 1, \dots, k$ . The null hypothesis is that there is no difference between the populations (the control group and the  $k$  intervention groups) in the survival at any time point. To test such null hypothesis, we use the *logrank*. Details of how logrank test is constructed can be found at [Bland, Martin and Douglas Altman \(2004\)](#). The test is merely a test of significance. Thus, it cannot provide an estimate of the size of the difference between the groups or a confidence interval. For these we must make some assumptions about the distribution of the data, for example exponential distribution.

## 3.3 Example: Acute myelogenous leukemia (aml) survival data

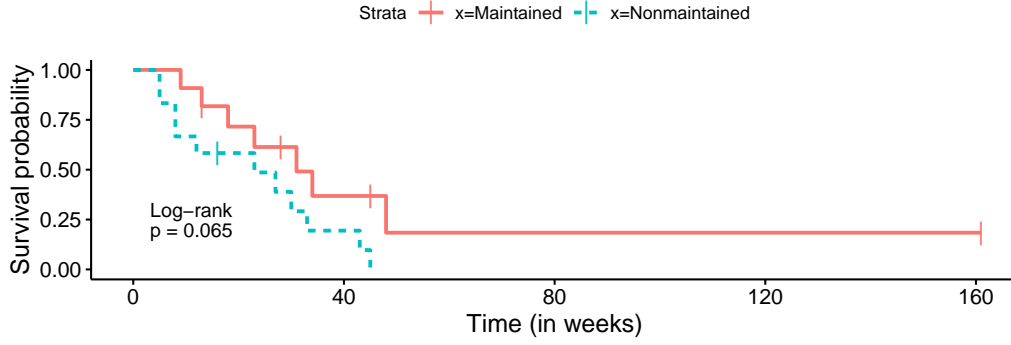
The "aml" data set is from the "survival" package in R, it is also known as "leukemia". The data set consist of 23 observations with 3 variables: *time* describing survival or censoring time (in weeks), *status* describing censoring status (0 is no-event or censored and 1 is an event/recurrence of aml) and *x* describing two levels of the treatment factor (Maintained chemotherapy or Nonmaintained chemotherapy). The data is shown below.

```
library(survival)
head(leukemia)

##   time status      x
## 1    9      1 Maintained
## 2   13      1 Maintained
## 3   13      0 Maintained
## 4   18      1 Maintained
## 5   23      1 Maintained
## 6   28      0 Maintained
```

Below is the KM estimate for each of the survival groups.

```
library(survival)
library(survminer)
ggsurvplot(survfit(Surv(time, status) ~ x, data = leukemia),
            pval = TRUE, pval.method = TRUE, linetype = "strata",
            censor.shape = 124, pval.size = 4, xlab = "Time (in weeks)")
```



The  $p$ -value of log-rank test for difference in survival curves is 0.065, indicating a rather weak evidence (assuming  $\alpha = 0.05$ ) that the intervention group (Maintained) performed better than the control group (Nonmaintained). The total sample size of 23 is rather modest (12 and 11 subjects respectively in control group and intervention group). So, maybe the power is rather low, thus not able to detect a difference.

## 4 Estimating sample size with logrank test

Recall the assumptions of the nonparametric logrank test for two treatment groups (control and intervention): (i) the subjects in two groups are homogeneous in all aspects except the treatment (identical property), (ii) the allocation of the treatment is based on randomization and not on characteristics of subjects (independent property), and (iii) survival function of each group follows exponential distribution (i.e., constant hazard rate for each group).

Assumption (iii) allows us to compare two survival curves by means of comparing the ratio of their hazard rates. Let  $S_0(t) = \exp(-\lambda_0 t)$  and  $S_1(t) = \exp(-\lambda_1 t)$  denote exponential survival curves for control group and intervention group, respectively. Then,  $\lambda_0$  and  $\lambda_1$  are the hazard rates of control and intervention, respectively. The hazard ratio (HR) is then defined as  $HR := \lambda_1/\lambda_0$ . The hypotheses are:

$$\begin{aligned} H_0 &: HR = 1 \\ H_1 &: HR \neq 1 . \end{aligned}$$

The above hypotheses are equivalent to:

$$\begin{aligned} H_0 &: \ln(HR) = 0 \\ H_1 &: \ln(HR) = \delta . \end{aligned}$$

In this parameterization, an effect size  $\delta$  is nicely quantified in term of the log-natural of the hazard ratio,  $\ln(HR)$ . An effect size of 0 in the null hypothesis means that the survival curves of the two groups are equal.

Two-sided sample size formula of two groups is given by (based on [Schoenfeld, David \(1981\)](#), see Section 3.2 for the details):

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{p_0 p_1 (\ln(HR))^2} \times \frac{1}{p_0 d_0 + p_1 d_1} \quad (1)$$

with

- $p_0$  and  $p_1$  are proportions of the subjects randomized to respectively control group and intervention group,
- $d_0$  and  $d_1$  are probabilities of the subjects to experience the event in respectively control group and intervention group (which are also called as mortality rates),
- $\alpha$  is the level of the test (probability of type I error),
- $1 - \beta$  is the power of the test.

When the allocations of the subjects randomized to either group is the same ( $p_0 = p_1 = 1/2$ ), then the formula (1) is simplified into

$$n = \frac{8 (z_{1-\alpha/2} + z_{1-\beta})^2}{(\ln(\text{HR}))^2} \times \frac{1}{(d_0 + d_1)} . \quad (2)$$

Notice that there is relationship between HR,  $d_0$  and  $d_1$ : given any two values, we can calculate the other one. See the example below for details.

## 4.1 Examples

### Example 1: working with hazard rates

Let us assume that a new drug (intervention) decreases the recurrence of back pain by 35% relative to a conventional drug (control). Thus, the hazard ratio is

$$\text{HR} = \frac{\lambda_1}{\lambda_0} = \frac{\lambda_0 - 0.35\lambda_0}{\lambda_0} = 1 - 0.35 = 0.65 ,$$

for any value of the hazard rate of control group  $\lambda_0$ . We want to estimate sample size needed to achieve 0.80 statistical power at 0.05 significance level, for the effect size of  $\delta = \ln(0.65)$ . We further assume an equal sample size for each group. Thus,  $p_0 = p_1 = 1/2$ .

Suppose further that a pilot study was conducted: two out of five subjects received conventional drug developed recurrence of back pain and the five subjects were observed for one month on average. This pilot study gave us an estimate of mortality rate of the control group,  $d_0 = 2/5 = 0.40$ .

What remains is an estimate of the mortality rate of the intervention group  $d_1$ . Given an estimate of the mortality rate of the control group  $d_0$  and a practical effect size  $\text{HR} = \frac{\lambda_1}{\lambda_0}$ , we can calculate an estimate for  $d_1$  as the following. First we note that the mortality rate is one minus the survival rate at time  $t = 1$  (duration of the study is one month):  $d := P(T < t) = 1 - S(1)$ . Furthermore, under the exponential model that  $S(t) = \exp(-\lambda t)$ , therefore  $S(1) = \exp(-\lambda)$ , we have  $d = 1 - \exp(-\lambda)$ . Or, equivalently  $\lambda = -\ln(1 - d)$ . Thus, we can calculate the hazard rate  $\lambda$  from the mortality rate  $d$  and vice versa. For the control group, given  $d_0 = 0.40$ , we get  $\lambda_0 = -\ln(1 - d_0) = -\ln(1 - 0.40) \approx 0.51$ . Given  $\lambda_0 = 0.51$  and  $\text{HR} = 0.65$ , the mortality rate of the intervention group is

$$d_1 = 1 - \exp(-\lambda_1) = 1 - \exp(-\lambda_0 \cdot \text{HR}) = 1 - \exp(-0.51 \cdot 0.65) = 1 - \exp(-0.33) \approx 0.28 .$$

Plugging in these values to the sample size formula (1)

```
my_nsize <- function(HR, d0, d1, P0, P1, alpha, beta){
  (qnorm(1-alpha/2) + qnorm(1-beta))^2 /
  (P0*P1*(P0*d0+P1*d1)*(log(HR))^2)
}
n_size <- my_nsize(0.65, 0.40, 0.28, 1/2, 1/2, 0.05, 0.20)
round(n_size, 2)

## [1] 497.59
```

gives us a total sample size of 497.59 for both groups, which we round up to 498 (that is, a balance size of 249 per group), with power of 0.80 and significant level of 0.05.

### Using R with Hmisc library

The calculation above can be done using *cpower* function in *Hmisc* package. The function *cpower* calculates the power of Cox (aka logrank) test, given the sample size and the other components of the sample size equation above. For our example, the calculation using *cpower* is given below.

```

library(Hmisc)
d0 <- 0.4
d1 <- 0.28
sample.size <- ceiling(n_size)
pow <- cpower(tref = 1, n = sample.size, mc = d0, r = 100*(d0 - d1)/d0,
              accrual = 0, tmin = 1, alpha = 0.05, pr = FALSE)
round(pow, 2)

## Power
## 0.81

```

Thus, for our example with equal sample size for each group and total of 498 subjects for both groups, using *cpower*, the power is given by 0.81. This slight discrepancy in the power (0.81 to 0.80) is due to ceiling up the sample size.

The parameterization of *cpower* function is slightly different than in our formula. In *cpower* the parameter *mc* = mortality rate of control group is our  $d_0$ , the parameter  $r = \%$  reduction in *mc* by intervention is nothing else but  $100(d_0 - d_1)/d_0$  and the parameter  $n$  = total sample size with equal size per group is  $n\_size = 498$ .

#### Online tool 1

We can carry out the calculation above using our shiny R interactive application [SampleSizeR](#) (see [Cherneva, Kalina and Reinhard Furrer and Bernadetta Tarigan \(2021\)](#)) where we apply the sample size formula (1) above.

#### Online tool 2

Another online tool is [powerandsamplesize.com](#). In this tool, the parameters are: (a) Hazard Ratio, that is 0.65; (b) Overall probability of event  $p_E$ , with our notation  $p_E = p_0 \cdot d_0 + p_1 \cdot d_1 = (1/2)(0.40 + 0.28) = 0.34$ ; and (c) Proportion of Sample in one group, with our notation is either  $p_0 = 1/2$  or  $p_1 = 1/2$ . At the output graph, scroll on the x-axis to see the corresponding exact total sample size  $n$ . With power of 0.80 and significant level of 0.05, we get a total sample size of 497. This slight discrepancy in total sample size (497 to 498) is due to software algorithm.

#### Online tool 3

Another online tool is [sample-size.net](#). The sample size calculation is conducted in two parts: (1) Calculate number of events given the significant level  $\alpha = 0.05$ , the type II error  $\beta = 1 - \text{power} = 0.20$ , either the  $p_0 = 1/2$  or the  $p_1 = 1/2$  (their notation is  $q_0$  and  $q_1$ ) and the hazard ratio of 0.65 (their notation is RH); (2) Using the above number of event (which resulting at 169), calculate sample size either given hazard rate of the control group  $\lambda_0 = 0.51$  (their notation is  $BER_0$ ) or given the median of the control group  $\ln(2)/\lambda_0$  (their notation is  $ST_0$ ) with censoring rate  $CR = 0$  and planned average length of follow-up  $FU = 1$ . We get a total sample size of 496. This slight discrepancy in total sample size (496 to 498) is due to software algorithm.

### **Example 2: working with medians**

In Example 1 above we work directly with the hazard ratio. However, sometimes we are more comfortable to work with median of survival time. This is easily can handle using the formula of the median  $m$  of an exponential survival time in term of the hazard parameter:  $m = \ln(2)/\lambda$ . Thus, the ratio of two medians are the inverse ratio of their hazard rates:

$$\frac{m_0}{m_1} = \frac{\ln(2)/\lambda_0}{\ln(2)/\lambda_1} = \frac{\lambda_1}{\lambda_0}.$$

Let assume that the new drug increase the median of the recurrence of back pain by 54% relative to a conventional drug. Thus,  $m_1 = m_0 + 0.54m_0 = 1.54m_0$  with  $m_1$  and  $m_0$  are respectively the median of the new drug and the median of the conventional drug. Plug-in the formula of the median in term of the hazard parameter, we



obtain that

$$\text{HR} = \frac{\lambda_1}{\lambda_0} = \frac{m_0}{m_1} = \frac{m_0}{1.54m_0} = 0.65 .$$

Thus, we can then proceed similarly to Example 1 above.

## 4.2 Derivation of sample size estimation based on two-samples logrank test

Let  $S$  denote the logrank statistic. We skip the details of formulation of  $S$ , but we follow the notations in Schoenfeld in *Biometrika* 1981 who showed the asymptotic distribution of  $S$  under the null and alternative hypotheses:

$$\begin{aligned} \text{under } H_0 : S &\sim N(0, 1) \\ \text{under } H_1 : S &\sim N(\delta\sqrt{p_0p_1d}, 1) \end{aligned}$$

with  $p_0$  and  $p_1$  are the proportions to be allocated into control group and intervention group respectively and  $d$  is the expected number of events (under the alternative hypothesis) from both groups.

By equating the critical value under  $H_0$  and the critical value under  $H_1$  we then can solve for  $d$ :

$$\begin{aligned} 0 + z_{1-\alpha/2} \cdot \sqrt{1} &= \delta\sqrt{p_0p_1d} - z_{1-\beta} \cdot \sqrt{1} \\ \sqrt{p_0p_1d} &= \frac{z_{1-\alpha/2} + z_{1-\beta}}{\delta} \\ d &= \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{p_0p_1\delta} . \end{aligned}$$

Replace  $\delta$  with  $\ln(\lambda_1/\lambda_0)$ , we obtained the first component of the sample size estimation formula.

Recall that  $d$  is the expected total number of events (under the alternative hypothesis from both groups). This quantity is sometimes denoted by  $n_{\text{events}}$ . Since not all subjects experience the event during the study period, the sample size calculation must take into account the probability of experiencing an event. This leads to the following relationship:

$$n = \frac{n_{\text{events}}}{\text{probability of the event}} .$$

Now, probability of the event is the sum of probability of an event of all subjects in control group and probability of an event of all subjects in intervention group:

$$\text{probability of the event} = p_0d_0 + p_1d_1 .$$

Thus, we obtain the formula

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{p_0 p_1 (\ln(\text{HR}))^2} \times \frac{1}{p_0d_0 + p_1d_1} .$$

## 5 Are you really interested in the survival time?

As we see in the Example 1 that sample size needed for analyzing survival time is a large number, typically of the magnitude of hundreds per group. In many cases, either this large number needed is not feasible or one confuses the difference between *overall-survival* and *survival-rate*. Overall-survival is a measure of probability of surviving over all time (it is a function of time) and survival-rate is a measure of the proportion/percentage of subjects who survived in a given period of time (it is a constant value). For the latter, the appropriate sample size is calculated based on the  $\chi^2$  test, the family of tests for categorical/nominal type of outcome, using the survival-rates (proportions) of both groups as the parameters. This calculation is also facilitated in [SampleSizeR](#). See also *Example 4.2.b* in [Tarigan, Bernadetta \(2022\)](#).

When either one of the survival-rates, denoted as  $\pi_0$  for the control group and  $\pi_1$  for the intervention group, is close to either zero or one, then one should use Fisher's exact test, instead of  $\chi^2$  test. Let  $n$  be the sample size calculated based on the  $\chi^2$  test. The correction for Fisher exact test is to replace  $n$  with

$$n' = \frac{n}{4} \cdot \left( 1 + \sqrt{1 + \frac{4}{n|\pi_0 - \pi_1|}} \right)^2$$

as shown by Wittes, Janet (2002) in equation (7C).

## References

- [1] Bland, Martin and Douglas Altman. The logrank test. <https://doi.org/10.1136/bmj.328.7447.1073>, 2004.
- [2] Cherneva, Kalina and Reinhard Furrer and Bernadetta Tarigan. SampleSizeR: calculate sample sizes within completely randomized design. <http://shiny.math.uzh.ch/git/reinhard.furrer/SampleSizeR/>, 2021.
- [3] Furrer, Reinhard and the Applied Statistics Group. *Statistical Modeling: An Excursion Through 14 Topics*. University of Zurich, Course STA121, 2020.
- [4] Schoenfeld, David. The asymptotic properties of nonparametric tests for comparing survival distributions. <https://doi.org/10.1093/biomet/68.1.316>, 4 1981.
- [5] Tarigan, Bernadetta. Planning Experiments and Sample Size Calculations. [https://www.math.uzh.ch/consulting/fileadmin/user\\_upload/Planning\\_experiments\\_and\\_sample\\_size\\_estimation.pdf](https://www.math.uzh.ch/consulting/fileadmin/user_upload/Planning_experiments_and_sample_size_estimation.pdf), 2022.
- [6] Wittes, Janet. Sample Size Calculations for Randomized Controlled Trials. <https://doi.org/10.1093/epirev/24.1.39>, 07 2002.

# Version Information

v1.1 04.02.2021

v1.2 19.01.2022 re-organize & add sections, add references & change style

```
print( sessionInfo(), locale=FALSE)

## R version 4.0.2 (2020-06-22)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Ubuntu 18.04.6 LTS
##
## Matrix products: default
## BLAS: /usr/lib/x86_64-linux-gnu/libf77blas.so.3.10.3
## LAPACK: /usr/lib/x86_64-linux-gnu/atlas/liblapack.so.3.10.3
##
## attached base packages:
## [1] stats graphics grDevices utils datasets methods base
##
## other attached packages:
## [1] Hmisc_4.4-1 Formula_1.2-3 lattice_0.20-41 survminer_0.4.9 ggpubr_0.4.0 ggplot2_3.3.5
## [7] survival_3.1-12 knitr_1.36
##
## loaded via a namespace (and not attached):
## [1] Rcpp_1.0.7 tidyr_1.1.4 png_0.1-7 zoo_1.8-9
## [5] assertthat_0.2.1 digest_0.6.25 utf8_1.1.4 R6_2.4.1
## [9] cellranger_1.1.0 backports_1.1.9 evaluate_0.14 highr_0.8
## [13] pillar_1.6.3 rlang_0.4.11 curl_4.3 readxl_1.3.1
## [17] rstudioapi_0.13 data.table_1.13.0 car_3.0-11 rpart_4.1-15
## [21] Matrix_1.3-4 checkmate_2.0.0 labeling_0.3 splines_4.0.2
## [25] stringr_1.4.0 foreign_0.8-80 htmlwidgets_1.5.4 munsell_0.5.0
## [29] broom_0.7.9 compiler_4.0.2 xfun_0.26 pkgconfig_2.0.3
## [33] base64enc_0.1-3 htmltools_0.5.2 nnet_7.3-16 tidyselect_1.1.0
## [37] htmlTable_2.0.1 tibble_3.1.5 gridExtra_2.3 km.ci_0.5-2
## [41] rio_0.5.16 fansi_0.4.1 crayon_1.4.1 dplyr_1.0.7
## [45] withr_2.4.2 grid_4.0.2 xtable_1.8-4 gtable_0.3.0
## [49] lifecycle_1.0.1 DBI_1.1.0 magrittr_2.0.1 KMsurv_0.1-5
## [53] scales_1.1.1 zip_2.1.1 stringi_1.4.6 carData_3.0-4
## [57] farver_2.0.3 ggsignif_0.6.3 latticeExtra_0.6-29 ellipsis_0.3.2
## [61] survMisc_0.5.5 generics_0.1.0 vctrs_0.3.8 openxlsx_4.1.5
## [65] RColorBrewer_1.1-2 tools_4.0.2 forcats_0.5.1 glue_1.4.2
## [69] purrr_0.3.4 jpeg_0.1-8.1 hms_1.1.1 fastmap_1.1.0
## [73] abind_1.4-5 colorspace_2.0-2 cluster_2.1.2 rstatix_0.7.0
## [77] haven_2.3.1
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