The function `ssCR()`: sample size calculation in the competing risks setting via simulations

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Abstract

The `R` function `ssCR()` computes power and sample size for randomized clinical trials that aim to compare cause specific hazards or cumulative incidence functions, in the competing risk setting. We assume that the logrank test or Gray's test (Gray, 1988) is used for these aims (both one-sided). Arbitrary cumulative incidence functions can be assumed for the main and competing events for patients of the two treatment groups (up to minor approximations). Arbitrary length of accrual period and end of follow-up can also be assumed. We assume that patients enter the study uniformly during the accrual period. These entirely specify the censoring distribution as no loss of follow-up is further assumed. Results are provided in the form of both numerical values and plots. The use of the function is demonstrated through examples. Computation details are also provided. This vignette is part of the supplementary material for the manuscript *"Sequential trials in the context of competing risks: concepts and case study, with R and SAS code"*.

Contents

1 Quick overview

The function computes power and sample size for (fixed, i.e. non sequential) randomized clinical trials that aim to compare cause specific hazards or cumulative incidence functions, in the competing risk setting. We assume that the logrank test or Gray's test (Gray, 1988) is used for these aims (both one-sided).

Power results are obtained by evaluating the proportion of significant test results, when applying the relevant tests to many simulated data sets. To generate these data sets, it is assumed that the cumulative incidence functions are piecewise linear between a grid of user specified values. Since an arbitrary fine grid is allowed, arbitrary close approximations to the true functions can be obtained (see the appendix Section 5 for computational details and Section 4 for examples).

2 Arguments of the function

The main function is `ssCR()`. As exemplified below in Sec. 4, an associated `plot` function is also provided to plot the results. The `ssCR()` function has the following arguments.

- `NMC`: number of Monte-Carlo simulation.
- `tau1`: length of accrual time.
- `tau2`: time of end of study (i.e. maximum possible follow-up time).
- `maxN`: maximum sample size for which we run the simulations.
- `minN`: minimum sample size.
- `byN`: 'by' statement to define the grid of sample sizes for which we run the simulations. The grid will be defined by `seq(from=minN,to=maxN,by=byN)`.
- `mypower`: power $(1 - \beta)$.
- `alpha`: type-I error (α).
- `pTreat`: proportion of patients included in the 'treatment/active group' (default is 0.5).
- `myseed`: seed, for reproducible simulation results.
- `times`: vector of times at which we specify the (expected) values of the cumulative incidence functions (CIF). One can provide a vector of an arbitrary length.
- `CIF10`: vector of expected values of the cumulative incidence function of the main event (1) in the control group (0), at each time of the input vector `times`.
- `CIF20`: similar to `CIF10` but for the competing event (2).
- `CIF11`: vector of expected values of the cumulative incidence function of the main event (1) in the treatment group (1), at each time of the input vector `times`.
- `CIF21`: similar to `CIF11` but for the competing event (2).

3 Output of the function

The function `ssCR()` returns an object of class "`ssCR`", which is a list. This list contains:

- `CompTime`: the total computation time.
- `input`: the list of the input values.
- `res`: the main results, which consist of:
  - `CSH`: the main results for the logrank test.
  - `FG`: the main results for Gray's test.
  - `ForPlot`: technical values for plotting the data generating characteristics using the `plot.ssCR` function.
  - `OneDataSet`: one simulated data set of sample size `maxN`.

  Both `CSH` and `FG` are lists. They contain the estimated power (`power.est`) and corresponding 95% confidence limits (`power.lower` and `power.upper`) for each sample size from `minN` to `maxN` and the estimated sample and associated 95% confidence limits (`n`), to reach the desired power specified in the input by `mypower`.

4 Examples

Three examples of the use of the function are provided below. The two main examples directly relate to the example study Neotrans discussed in detail in the manuscript. They are presented in Sec. 4.1 and 4.2 below. They aim to reproduce and assess the validity of the sample sizes calculation presented in the manuscript (for a fixed trial, i.e. non sequential).
The third example illustrates how the `ssCR()` function can further provide sample size calculations for trials with delayed entries and limited follow-up, which leads to observations of right censored data. It is presented in Sec. 4.3 below.

4.1 Neotrans: cause specific hazard approach

Let us consider the cause specific hazard approach for the example study Neotrans of the main manuscript.
First, we set the main parameter values needed for the sample size calculation. See the main manuscript for details about how the values below are derived from previous clinical knowledge.

```
myNMC <- 5000     # Number of simulated datasets (Monte Carlo)
HR <- 2.16        # Hazard Ratio
csh10 <- 0.0246   # cause-specific hazard for the main event, control group
csh11 <- csh10*HR # cause-specific hazard for the main event, treatment group
csh20 <- 0.0098   # cause-specific hazard for the competing event, treatment group
csh21 <- csh20    # cause-specific hazard for the competing event, treatment group
```

Second, from the above values, we compute the expected values of the cumulative incidence functions of each event and each treatment group for a fine grid of times, for a large time interval. Hence, the piecewise linear approximation made by our `R` function `ssCR()` will be very good. See the main manuscript for the mathematical details corresponding to the code block below.

```
mytimes <- c(seq(from=0.1,to=50,by=0.1),
             seq(from=51,to=99,by=1),
             seq(from=100,to=145,by=5),
             seq(from=150,to=300,by=50)) # times at which we specify CIF values
CIF <- function(t,csh1,csh2){csh1/(csh1+csh2)*(1-exp(-(csh1+csh2)*t))}
myCIF10 <- sapply(mytimes,CIF,csh1=csh10,csh2=csh20) # CIF values:  main event, control
myCIF20 <- sapply(mytimes,CIF,csh1=csh20,csh2=csh10) # CIF values:  competing event
myCIF11 <- sapply(mytimes,CIF,csh1=csh11,csh2=csh21) # CIF values:  main event, treated
myCIF21 <- sapply(mytimes,CIF,csh1=csh21,csh2=csh11) # CIF values:  competing event
```

We now call the function `ssCR()` for the sample size calculation (it takes a few minutes to run).

```
ResSSCR <- ssCR(NMC=myNMC,  # number of simulated datasets
                tau1=0,     # length of accrual period
                tau2=Inf,   # maximum follow-up time
                maxN=65,    # maximum sample size
                minN=45,    # minimum sample size
                byN=1,      # increment for grid of sample sizes
                mypower=0.80,     # power
                alpha=0.05,       # Type-I error
                myseed=20180616,  # seed for reproducibility
                times=mytimes,    # times at which we specify CIF values
                pTreat=0.5,       # randomization ratio
                CIF10=myCIF10,    # CIF values:  main event, control
                CIF20=myCIF20,    # CIF values:  competing event, control
                CIF11=myCIF11,    # CIF values:  main event, treated
                CIF21=myCIF21)    # CIF values:  competing event, treated
```

We can plot the main characteristics of the simulated data by calling:

```
plot(ResSSCR,type="data generation",myxlim=c(0,35))
```

This results in Figure 1. One can visualize the expected cumulative incidence and cause-specific hazard functions for both causes and both treatment groups (red and green curves, left axes), the cause specific hazard ratios and the subdistribution hazard ratio (black curves, right axes). These are some of the most important characteristics of the simulated data.

As expected, one can notice that the cause specific hazard ratios are constant over time for the main and competing event (but not the subdistribution hazard ratio) and that there is no treatment effect assumed on the competing risk cause-specific hazard. See appendix Sec. 5.2 below for the mathematical details to compute these curves from the input values of the function. Furthermore, one can remark that using a fine grid of times results in cumulative incidence plots where the piecewise linear approximation is very good and barely noticeable. Besides, because here we assume infinite follow-up, the censoring survival function is equal to one at any time.

To visualize the power of the logrank test, to test for a treatment effect on the cause-specific hazard of the main event, for sample sizes from `minN`=45 to `maxN`=65, one can call:

```
plot(ResSSCR,type="CSH")
```

This results in Figure 2. Here we can see that the sample size needed to achieve a power of 80% is estimated to be $n = 59$, based on the `NMC`=5000 simulated data sets. The gray area around the

estimated power curve displays the exact (binomial) confidence intervals for the power. It shows to which extent NMC=5000 simulated data sets can produce accurate estimates of the power and sample size. By inverting the curves of the confidence intervals for the power, a confidence interval for the sample size is computed as 57–60. Of course, one can make this interval become arbitrary narrow, by increasing the number of simulated data sets NMC. The only drawback of increasing NMC is the increase in computation time. The details of the algorithm to simulate the data are presented in Sec. 5.3 below.

The sample size estimated from these simulations is different (although not very different) from $n = 54$ (rounded upwards) computed using the Schoenfeld (1983) formula. The formula to compute this sample size is explained in the main manuscript and corresponds to this code:

```
zalpha <- qnorm(0.05)
zbeta <- qnorm(1-0.80)
p10 <- max(myCIF10)
p11 <- max(myCIF11)
nSchoenfeld <- (((zalpha+zbeta)/log(HR)))^2/((0.5*p10 + (1-0.5)*p11)*(0.5*(1-0.5)))
nSchoenfeld
```

which returns

```
[1] 53.48142
```

The difference between the sample size computed by simulations and by the Schoenfeld formula probably comes from the fact that the large sample approximation of the Schoenfeld formula is a little rough in our context. Indeed, $n = 54$ is not very large and so the large sample size approximation of Schoenfeld (1983) might not be very precise here. However, the simulations suggest that the sample size obtained from the Schoenfeld formula leads to a power of about 76%, which is not very far from the targeted 80%. One can see this result directly on Figure 2 and by running the code:

```
round(data.frame(Est=ResSSCR$res$CSH$power.est,
           Lower=ResSSCR$res$CSH$power.lower,
           Upper=ResSSCR$res$CSH$power.upper)*100,1)["54",]
```

which returns

```
    Est Lower Upper
54 76.4  75.2  77.6
```

showing that the estimated power for $n = 54$ is 76.4% (95% CI: 75.2-77.6).

4.2 Neotrans: cumulative incidence approach

Let us now consider the example of Neotrans with the cumulative incidence approach. First, we set the main parameter values needed for the sample size calculation. Here again, see the main manuscript for details about how the values below were obtained from previous clinical knowledge.

```
myNMC <- 5000 # Number of simulated datasets (Monte Carlo)
SHR <- 2      # Expected subdistribution hazard ratio
thet <- 35    # The specific time t at which we provide the value of CIFs
CIF10t <- 0.5 # Value of cumulative incidence function (CIF) at t for the control group
p10 <- 0.75   # Value of CIF at t=Inf, for the main event, in control group
```

Second, from the above values, we compute the expected values of the cumulative incidence functions of each event and each treatment group for a fine grid of times, for a large time interval. Hence, the piecewise linear approximation made by our R function `ssCR()` will be very good. Because the above values do not entirely specify the data generation mechanism (because we only assume a semi-parametric model), a few (minor) additional assumptions are needed to simulate the data. Although different assumptions could be chosen, it is important to note that these additional assumptions do not matter asymptotically (Latouche et al., 2004). See Sec. 5.4 below for the mathematical details corresponding to the code block below.

```
mytimes <- c(seq(from=1,to=54,by=1),
             seq(from=55,to=80,by=5),
             seq(from=100,to=200,by=25),300) # times at which we specify CIF values
theta10 <- (1/(-thet))*log(1-CIF10t/p10)
theta20 <- theta21 <- theta10
p11 <- 1-(1-p10)^SHR       # value of CIF of main event at t=Inf in the treatment group
CIF11t <- 1-(1-CIF10t)^SHR # value of CIF at t for the treatment group
myCIF10 <- 1-(1-p10*(1-exp(-theta10*mytimes))) # CIF values:  main event, control
myCIF20 <- (1-p10)*(1-exp(-theta20*mytimes))   # CIF values:  competing event, control
myCIF11 <- 1-(1-myCIF10)^SHR                   # CIF values:  main event, treated
myCIF21 <- (1-p11)*(1-exp(-theta21*mytimes))   # CIF values:  competing event, treated
```

We now call the function `ssCR()` for sample size calculation (it takes a few minutes to run).

```
ResSSCR <- ssCR(NMC=myNMC,  # number of simulated datasets
                tau1=0,     # length of accrual period
                tau2=Inf,   # maximum follow-up time
                maxN=70,    # maximum sample size
                minN=50,    # minimum sample size
                byN=1,      # increment for grid of sample sizes
                mypower=0.80,     # power
                alpha=0.05,       # Type-I error
                myseed=20180616,  # seed for reproducibility
                times=mytimes,    # times at which we specify CIF values
                pTreat=0.5,       # randomization ratio
                CIF10=myCIF10,    # CIF values:  main event, control
                CIF20=myCIF20,    # CIF values:  competing event, control
                CIF11=myCIF11,    # CIF values:  main event, treated
                CIF21=myCIF21)    # CIF values:  competing event, treated
```

We plot the main characteristics of the simulated data by calling:

```
plot(ResSSCR,type="data generation",myxlim=c(0,35))
```

This results in Figure 3. As expected, one can notice that the subdistribution hazard ratio is constant over time (but not the cause specific hazard ratios). See appendix Sec. 5.2 for the mathematical details to compute these curves from the input values of the function.

To visualize the power of Gray's test for sample sizes from `minN`=50 to `maxN`=70, one can call:

```
plot(ResSSCR,type="Gray")
```

This results in Figure 4, where we can see that the estimated sample from `NMC`=5000 simulated data sets is $n = 63$. The 95% confidence interval for the sample size is 60-64. One can of course obtain a

more precise sample size estimate and a narrower confidence interval, if needed, by increasing the number of simulated data sets.

The results of these simulations are consistent with those obtained from the Schoenfeld formula, which leads to $n = 62$ (rounded upwards), as explained in the main manuscript and computed by:

```
zalpha <- qnorm(0.05)
zbeta <- qnorm(1-0.80)
nSchoenfeld <- (((zalpha+zbeta)/log(SHR)))^2/((0.5*p10 + (1-0.5)*p11)*(0.5*(1-0.5)))
nSchoenfeld
```

which returns

```
[1] 61.00472
```

4.3 Additional example with censoring

We now consider an additional example with right censoring, due to delayed entries and limited follow-up. We consider the same setting as the example study Neotrans with the cumulative incidence approach (Sec. 4.2), except that we now assume that 1) the study lasts 35 days only and 2) patients enter the study "at random" during the first 15 days (specifically, we assume a uniform distribution over $[0, 15]$ for the entry times).

After having set the main parameter values needed for the sample size calculation and computed the expected values of the cumulative incidence functions as in the previous Section 4.2, we can simply run:

```
ResSSCR <- ssCR(NMC=myNMC,  # number of simulated datasets
                tau1=15,    # length of accrual period
                tau2=35,    # maximum follow-up time
                maxN=105,   # maximum sample size
                minN=85,    # minimum sample size
                byN=1,      # increment for grid of sample sizes
                mypower=0.80,     # power
                alpha=0.05,       # Type-I error
                myseed=20180616,  # seed for reproducibility
                times=mytimes,    # times at which we specify CIF values
                pTreat=0.5,       # randomization ratio
                CIF10=myCIF10,    # CIF values:  main event, control
                CIF20=myCIF20,    # CIF values:  competing event, control
                CIF11=myCIF11,    # CIF values:  main event, treated
                CIF21=myCIF21)    # CIF values:  competing event, treated
```

We plot the main characteristics of the simulated data by calling:

```
plot(ResSSCR,type="data generation",myxlim=c(0,35))
```

This results in Figure 5. As expected, this Figure is similar to that of Figure 3, except from the censoring distribution. As expected, we can see that the probability of not being censored is 1 until 35-15=20 days and then decreases to reach 0 at 35 days (end of follow-up). To visualize the power of Gray's test for sample sizes from `minN`=85 to `maxN`=105, one can call:

```
plot(ResSSCR,type="Gray")
```

This results in Figure 6, where we can see that the estimated sample from `NMC`=5000 simulated data sets is $n = 95$ (95% CI 92-97). As expected, this is larger than $n = 63$ obtained in Sec. 4.2 when assuming no censoring, that is, a sufficiently long follow-up ($\approx \infty$) to observe the time to one of the competing events for all subjects.

5 Appendix: computational details

5.1 Model and notations

To simulate competing risks data with the `ssCR` function, we proceed as follows.
We assume that the generated data $\{(\widetilde{T}_i, \widetilde{\eta}_i, Z_i), i = 1, \ldots, n\}$ consist of n i.i.d replicates of $(\widetilde{T}, \widetilde{\eta}, Z)$, where $\widetilde{T} = \min(T, C)$ denotes the observed time, C the censoring time, $\widetilde{\eta} = \eta \cdot \Delta$ the observed event type, with $\Delta = \mathbb{1}\{T \leq C\}$ and Z the treatment group (1 if treated, 0 otherwise).

Let $F_j^z(t) = \mathbb{P}(T \leq t, \eta = j | Z = z)$ denote the cumulative incidence function of event j at time t for the treatment group $Z = z$. For $j = 1, 2$ and $z = 0, 1$, we assume the function $F_j^z(\cdot)$ to be piecewise linear on $[0, t_K]$, with t_K large enough such that $F_1^z(t_K) + F_2^z(t_K) \approx 1$ for $z = 0, 1$. Let $t_1 < \cdots < t_K$ be K time points chosen to specify each function $F_j^z(\cdot)$, $j = 1, 2$, $z = 0, 1$, through the values $F_j^z(t_k)$, $k = 1, \ldots, K$. Let $t_0 = 0$. For $t \in [0, t_K]$, we assume

$$F_j^z(t) = a_{jzi_t} + b_{jzi_t}(t - t_{i_t - 1})$$

where $i_t = 1 + \sum_{k=1}^{K} \mathbb{1}\{t \geq t_k\}$ equals 1 if $t \in [0, t_1[$, 2 if $t \in [t_1, t_2[$ and so on and

$$a_{jzi_t} = F_j^z(t_{i_t - 1}) \quad \text{and} \quad b_{jzi_t} = \frac{F_j^z(t_{i_t}) - F_j^z(t_{i_t - 1})}{t_{i_t} - t_{i_t - 1}} \ .$$

5.2 Key functions to characterize the data generation

The survival function for group $Z = z$ at time t is

$$S^z(t) = \mathbb{P}(T > t | Z = z) = 1 - F_1^z(t) - F_2^z(t) \ .$$

Because we work with piecewise linear cumulative incidence functions, the relationships below hold. The cause-j-specific hazard function for group $Z = z$ at time t is

$$\begin{aligned} \lambda_j^z(t) &= \lim_{dt \to 0} \mathbb{P}(t \leq T \leq t + dt, \eta = j | T \geq t, Z = z)/dt \\ &= \frac{\partial F_j^z(t)}{\partial t} \Big/ S^z(t) \\ &= \frac{b_{jzi_t}}{1 - a_{\bullet zi_t} - b_{\bullet zi_t}(t - t_{i_t - 1})}, \end{aligned}$$

where $a_{\bullet z i_t} = a_{1 z i_t} + a_{2 z i_t}$ and $b_{\bullet z i_t} = b_{1 z i_t} + b_{2 z i_t}$.
The subdistribution hazard function for group $Z = z$ at time t is (for cause j)

$$\begin{aligned}\widetilde{\lambda}_j^z(t) &= \lim_{dt \to 0} \mathbb{P}\big(t \le T \le t + dt, \eta = j \,|\, \{T \ge t\} \cup \{T \le t, \eta \ne j\}, Z = z\big)/dt \\ &= \frac{\partial F_j^z(t)}{\partial t} \Big/ \big\{1 - F_j^z(t)\big\} \\ &= \frac{b_{j z i_t}}{1 - a_{j z i_t} - b_{j z i_t}(t - t_{i_t - 1})} \ .\end{aligned}$$

5.3 Data generation

For each subject i with $Z_i = z_i$, we generate $\widetilde{T}_i$ and $\widetilde{\eta}_i$ as follows.

1. Generate U_i from a uniform distribution on $[0, 1]$.
2. Compute $T_i = \{U_i - 1 + S^{z_i}(t_{l_i - 1})\}/b_{\bullet z l_i} + t_{l_i - 1}$ if $l_i \le t_K$ (that is, solve $1 - S^{z_i}(T_i) = U_i$) and $T_i = t_K + 1$ otherwise, where $l_i = 1 + \sum_{k=1}^{K} \mathbb{1}\{U_i \ge S^{z_i}(t_k)\}$.
3. Generate $\eta_i = 1 + B_i$, where B_i is generated from a Bernoulli random variable with probability of success $\lambda_2^{z_i}(T_i)/\{\lambda_1^{z_i}(T_i) + \lambda_2^{z_i}(T_i)\}$ if $T_i \le t_K$ and $1/2$ otherwise.
4. Generate the entry time E_i from a uniform distribution on $[0, \tau_1]$, where τ_1 is the length of the accrual period.
5. Compute $T_i = \min(\tau_2 - E_i, T_i)$, where τ_2 is the time of the end of the study.
6. Compute $\Delta_i = \mathbb{1}\{T_i = \widetilde{T}_i\}$ and $\widetilde{\eta}_i = \eta_i \cdot \Delta_i$.

See e.g. Beyersmann et al. (2011, p. 45) for a similar algorithm.

5.4 Proportional subdistribution hazard model

Here we describe how we simulate data for the example of Sec. 4.2. As already mentioned in the above Sec. 4.2, because a semi-parametric model does not entirely specify the data generation mechanism, a few (minor) additional assumptions are needed to simulate some data. Below we present the fully specified data generation mechanism that we have used.

We use a similar model to that used by Fine and Gray (1999) for their simulations. First, we model the cumulative incidence function of the main event. For the control group ($z = 0$), we model

$$F_1^0(t) = p_{10}\Big\{1 - \exp(-\theta_{10} t)\Big\} \ .$$

Note that $F_1^0(\infty) = p_{10}$ and that $\theta_{10} = -\log\big\{1 - F_1^0(t)/p_{10}\big\}/t$ for all t. This implies that the values of the two model parameters p_{10} and θ_{10} are uniquely defined from three values: a time t and the values of $F_1^0(\cdot)$ at t and at ∞.

Let $\widetilde{\gamma}$ be the log of the subdistribution hazard ratio, i.e. $\exp(\widetilde{\gamma}) = \widetilde{\lambda}_1^1(t)/\widetilde{\lambda}_1^0(t)$ for all t. This corresponds to the following model for the treatment group ($z = 1$)

$$F_1^1(t) = 1 - \Big[1 - p_{10}\Big\{1 - \exp(-\theta_{10} t)\Big\}\Big]^{\exp(\widetilde{\gamma})} \ .$$

Let us now consider the cumulative incidence function of the competing event. For the control group ($z = 0$), we model

$$F_2^0(t) = (1 - p_{10})\Big\{1 - \exp(-\theta_{20} t)\Big\} \ .$$

Note that $F_2^0(\infty) = 1 - p_{10}$ and that the equation $\theta_{20} = -\log\big\{1 - F_2^0(t)/(1 - p_{10})\big\}/t$, which holds for all t, can be used to link the value of the parameter θ_{20} to that of the cumulative incidence $F_2^0(t)$ at any time t. For the treatment group ($z = 1$), we model

$$F_2^1(t) = (1 - p_{10})^{\exp(\widetilde{\gamma})} \cdot \Big\{1 - \exp(-\theta_{21} t)\Big\} \ .$$

The equation $\theta_{21} = -\log\big\{1 - F_2^1(t)/(1 - p_{10})^{\exp(\widetilde{\gamma})}\big\}/t$ can be used to link the value of the parameter θ_{21} to that of the cumulative incidence $F_2^1(t)$ at any time t.

References

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Schoenfeld, D. A. (1983). Sample-size formula for the proportional-hazards regression model. *Biometrics*, 39(2):499–503.

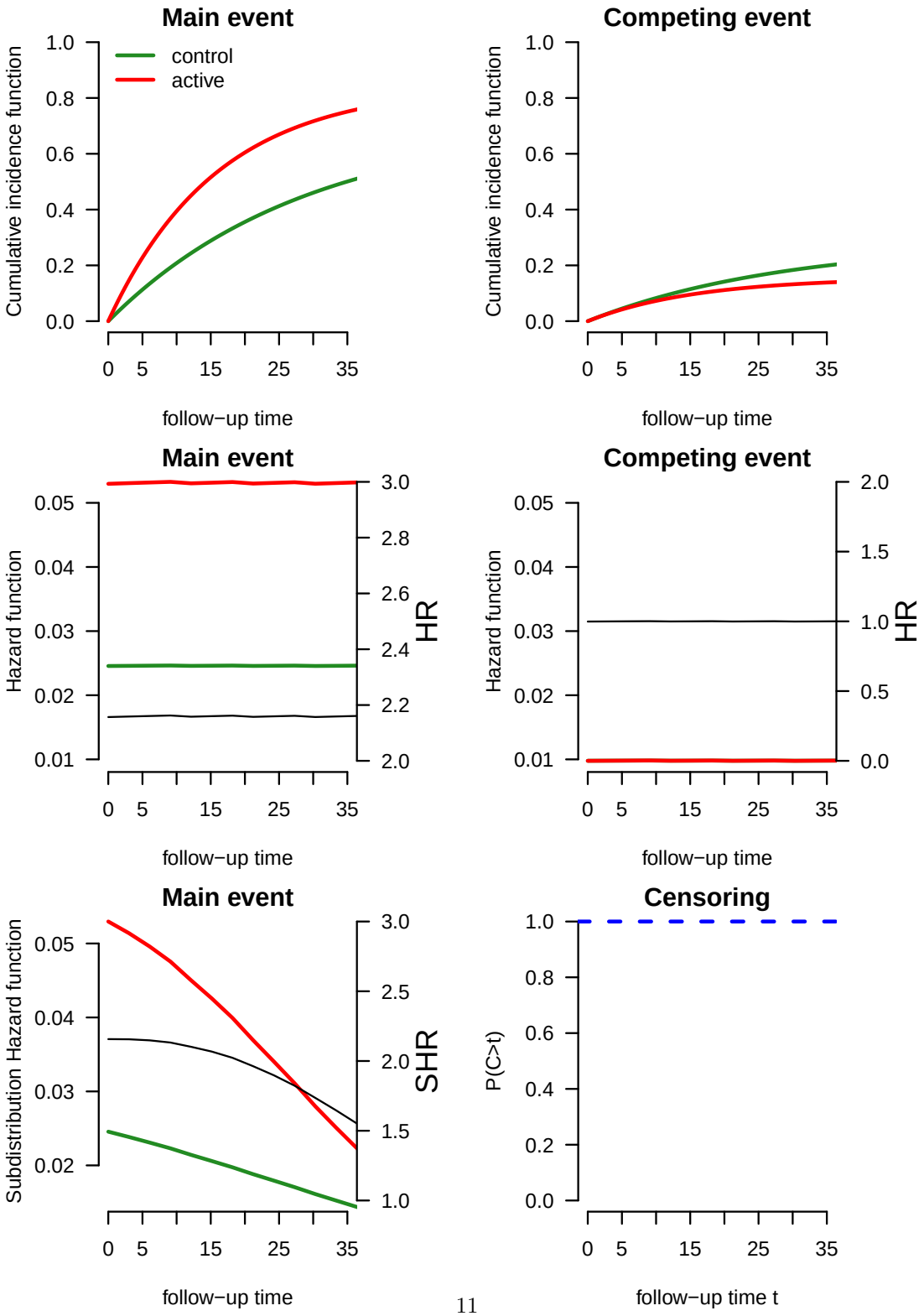

Figure 1: Assumed data generating functions for the Neotrans cause-specific hazard approach example.

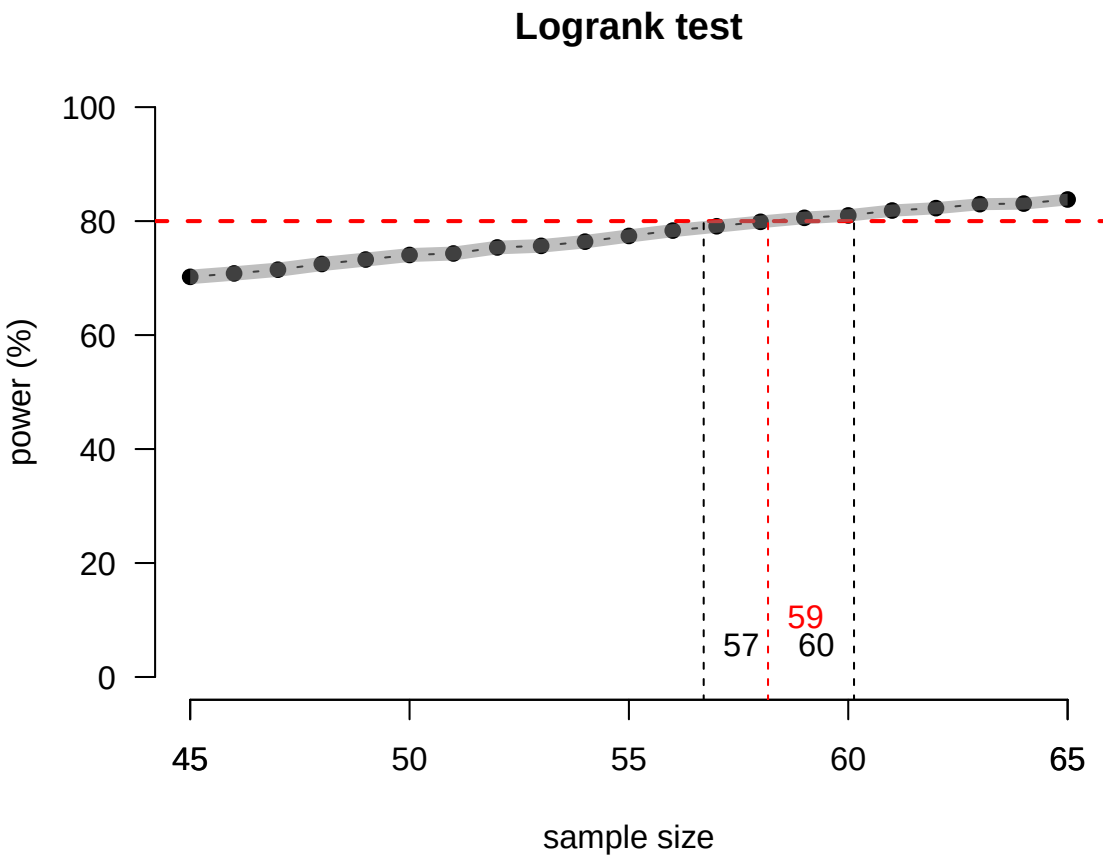

Figure 2: Power of logrank test, Neotrans cause-specific approach example.

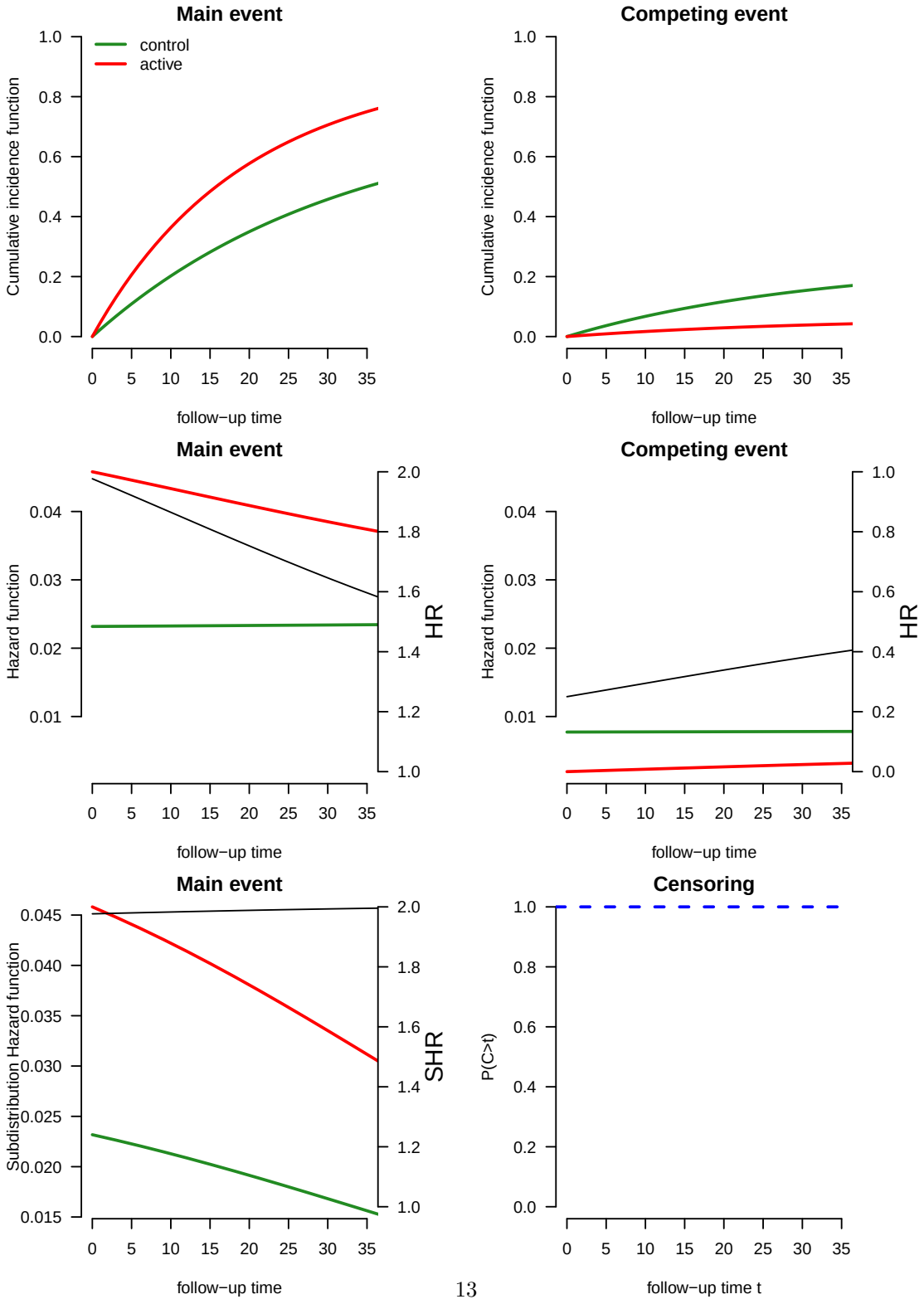

Figure 3: Assumed data generating functions for the Neotrans cumulative incidence approach example.

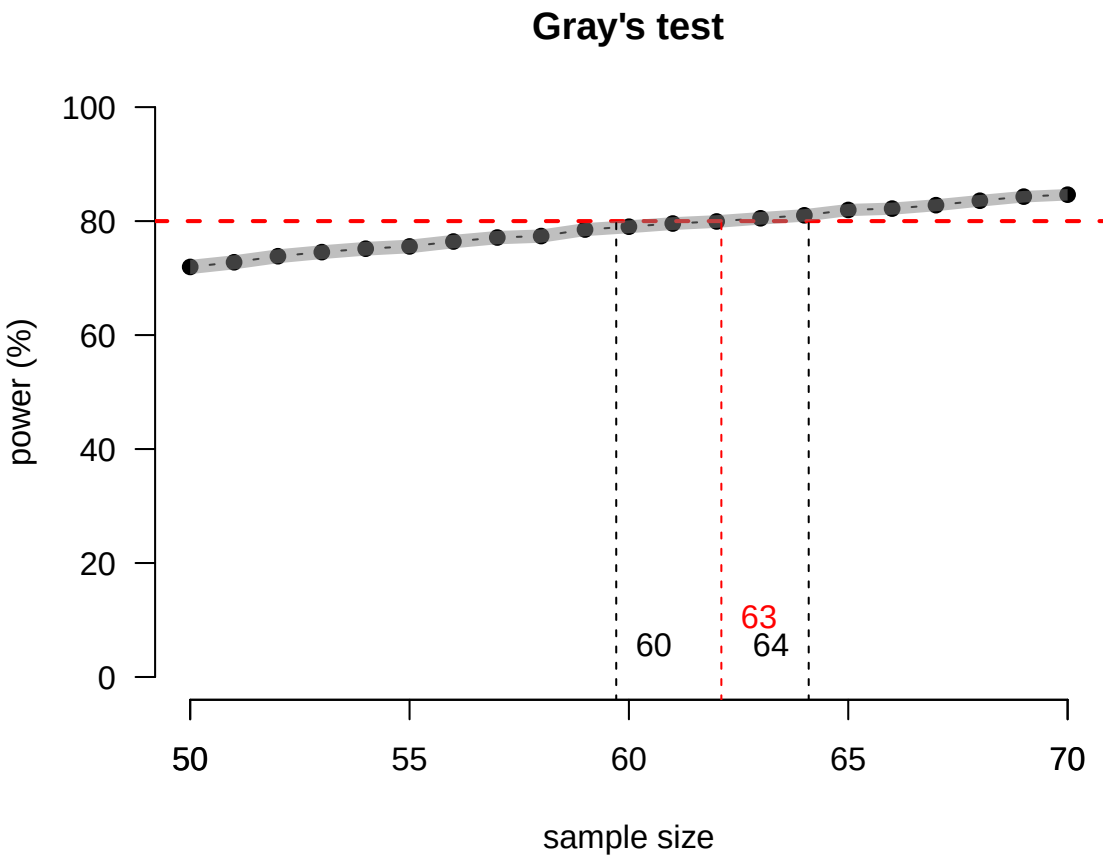

Figure 4: Power of Gray's test, Neotrans cumulative incidence approach example.

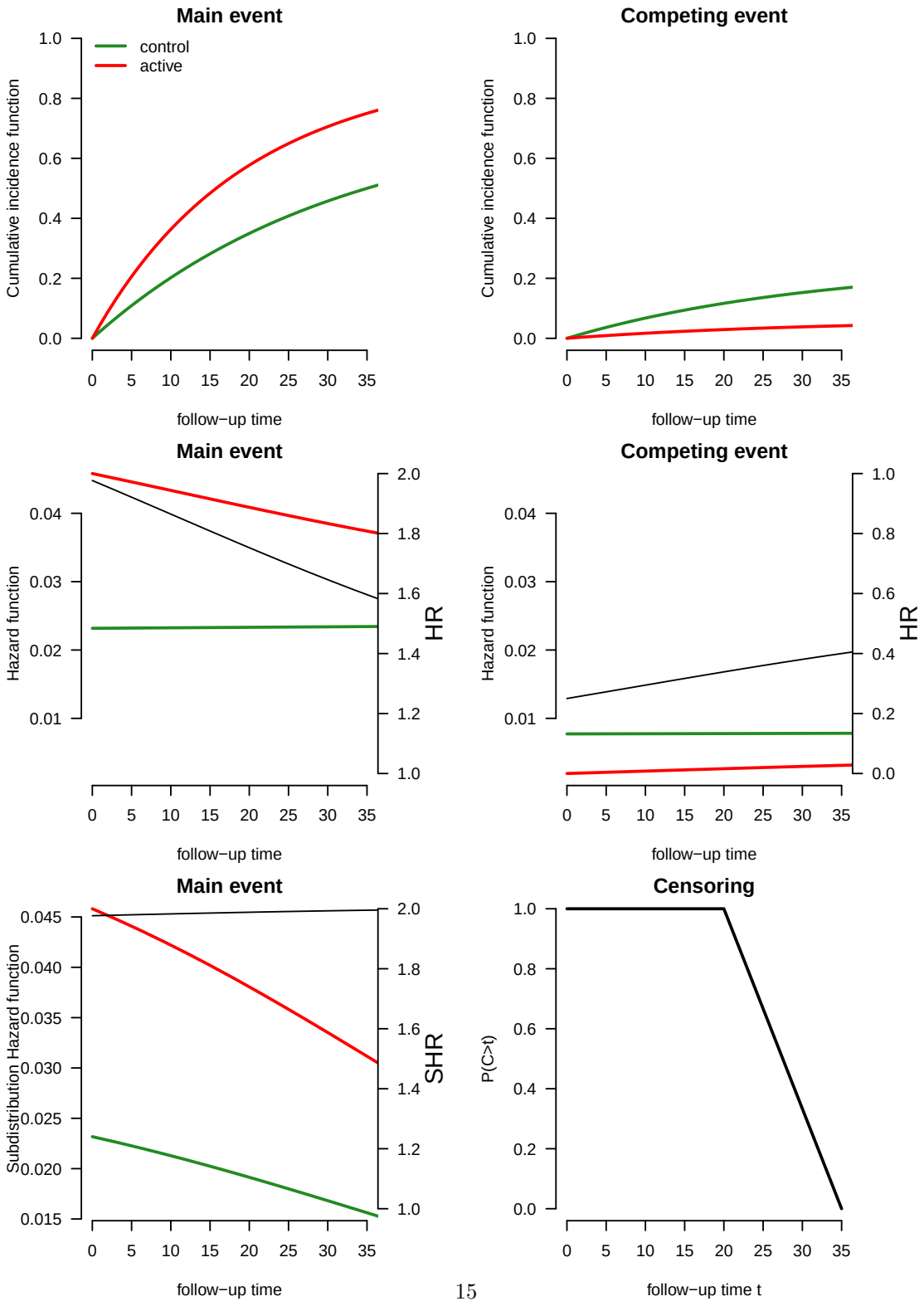

Figure 5: Assumed data generating functions for the additional example with censoring.

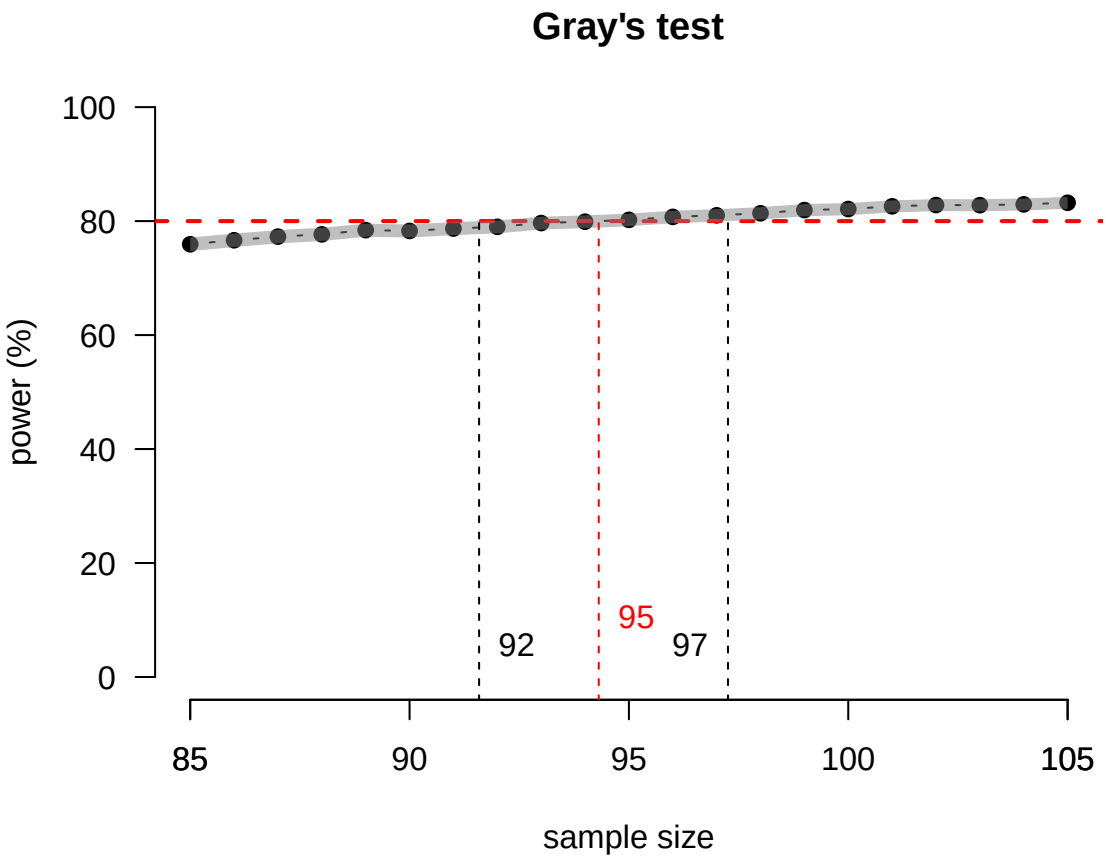

Figure 6: Power of Gray's test, additional example with censoring.