Published in final edited form as:

Comput Methods Programs Biomed. 2014 January ; 113(1): . doi:10.1016/j.cmpb.2013.10.001.

NPHMC: An R-package for Estimating Sample Size of Proportional Hazards Mixture Cure Model

Chao Cai^{a,*}, Songfeng Wang^b, Wenbin Lu^c, and Jiajia Zhang^a

^aDepartment of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC 29208, USA

^bHealth and Civilian Solutions division, General Dynamics Information Technology, 1401 50th St, West Des Moines, Iowa 50266, USA

^cDepartment of Statistic, University of North Carolina, Raleigh, NC 27695, USA

Abstract

Due to advances in medical research, more and more diseases can be cured nowadays, which largely increases the need for an easy-to-use software in calculating sample size of clinical trials with cure fractions. Current available sample size software, such as PROC POWER in SAS, Survival Analysis module in PASS, powerSurvEpi package in R are all based on the standard proportional hazards (PH) model which is not appropriate to design a clinical trial with cure fractions. Instead of the standard PH model, the PH mixture cure model is an important tool in handling the survival data with possible cure fractions. However, there are no tools available that can help design a trial with cure fractions. Therefore, we develop an R package NPHMC to determine the sample size needed for such study design.

Keywords

Proportional hazards mixture cure model; Power; Sample size; Weighted log-rank test; R package

1. Introduction

Sample size calculation is an important component in designing randomized controlled clinical trials with time-to-event endpoints. Assuming constant hazard ratio between the treatment and control arm, the following sample size formula based on the standard PH model has been widely used in practice [5, 6]:

$$n = \frac{(Z_{\alpha/2} + Z_{\theta})^2}{p(1-p)\beta_0^2 P(\delta=1)}, \quad (1)$$

© 2013 Elsevier Ireland Ltd. All rights reserved.

*Corresponding author caic@email.sc.edu (Chao Cai).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

7. Availability

The package NPHMC and the relevant documentation can be freely downloaded from CRAN webpage <http://cran.r-project.org/package=NPHMC>.

where $1 - \alpha$ specifies the level of significance of statistical test and $1 - \theta$ specifies the power of statistical test; $Z_{\alpha/2}$ and Z_θ are the upper $\alpha/2$ and θ percentiles of the standard normal distribution, respectively; p is the proportion of patients being assigned to the treatment arm; β_0 is the log-hazard ratio between treatment and control arms; δ is the censoring indicator (1 for failure and 0 for censoring); and $P(\delta = 1)$ is the probability of failure. Assuming $S_C(t) = P(C > t)$ is the survival function of censoring time and $f_0(t)$ is the density function of survival times for uncured patients in the control arm, $P(\delta = 1) = \int_0^\infty S_C(t) f_0(t) dt$. Formula (1), with a common assumption that $f_0(t)$ follows the exponential distribution and $S_C(t)$ comes from a uniform distribution, has been implemented in the most software, such as PROC POWER in SAS.

One unstated assumption of the standard PH model is that all individuals under study are susceptible to the adverse event of interest, and they will experience the event eventually if there was no censoring. However, more and more patients will be cured nowadays due to the advances in recent medical research. That is, those patients may never experience the event even after a sufficient follow-up period. The mixture cure model [3, 4, 7] is particularly designed to handle the dataset with a cure fraction. Unlike the standard survival model, the mixture cure model has two components in order to model the cure probability and survival probability of uncured patients.

Assume $S_j^*(\cdot)$ and $S_j(\cdot)$ denote the overall survival function and survival function of uncured patients respectively, and $\pi_j(0 < \pi_j < 1)$ is the cure rate in the arm j , where $j = 0$ for the control arm and $j = 1$ for the treatment arm. The mixture cure model can be written as

$$S_j^*(t) = \pi_j + (1 - \pi_j) S_j(t). \quad (2)$$

Specifically, the PH mixture cure model is designed by assuming the PH model for uncured patients and the logistic regression for cure probability.

In this paper, we design an R package NPHMC to implement the sample size calculation proposed in [8]. Because the sample size formula based on the PH mixture cure model (2) includes the sample size calculation based on the standard PH model, the R package NPHMC is an extension of the exiting sample size software for designing survival trial. In the next Section, we outline the computational method. The R function and its arguments are described in Section 3. A simulation study comparing parametric with nonparametric sample size calculation is discussed in Section 4. Two examples are provided to illustrate the usage of NPHMC package in Section 5. Some conclusions are given in Section 6.

2. Method

Let T denote the observed times, which is the minimum of the failure time and censoring time. We assume that the censoring is independent. Let $\lambda_j^*(\cdot)$ denote the overall hazard function and $\lambda_j(\cdot)$ denote the hazard function of uncured patients for the arm j , $j = 0, 1$ respectively. The PH mixture cure model (2) assumes the constant hazard ratio between the treatment and control arms, that is $\lambda_1(t) = e^{\beta_0} \lambda_0(t)$ and the difference of log odds ratio of cure rates between two arms is a constant, which can be written as $\text{logit}(\pi_1) = \text{logit}(\pi_0) + \gamma_0$, where β_0 and γ_0 are unknown parameters. When $\pi_0 = \pi_1 = 0$, it reduces to the standard PH model.

For a survival trial with a proportion of patients cured, we are interested in testing $H_0: \beta_0 = \gamma_0 = 0$, and its alternative hypothesis, H_a , is at least one equality does not hold. That is, it can accommodate various scientific hypotheses, such as $H_a: \beta_0 > 0, \gamma_0 = 0$, the treatment has effects on both cure rate and survival of uncured patients; $H_a: \beta_0 > 0, \gamma_0 > 0$, the treatment

only has effects on survival probability of uncured patients; and $H_a: \beta_0 = 0, \gamma_0 = 0$, the treatment only has effects on the cure rate. To derive the power and sample size calculation for the PH mixture cure model, we need to consider a series of local alternatives. Wang et al. [8] has shown that to achieve a power of $1 - \theta$, the total sample size for the PH mixture cure model based on the log rank test can be determined by

$$n = \frac{(Z_{\theta} + Z_{\alpha/2})^2 \int_0^{\infty} S_C(t) f_0(t) dt}{p(1-p) \beta_0^2 (1 - \pi_0) \left\{ \int_0^{\infty} m(\gamma_0, \beta_0, \pi_0) S_C(t) f_0(t) dt \right\}^2}, \quad (3)$$

where $m(\gamma_0, \beta_0, \pi_0) = \pi_0 \{ \gamma_0 / \beta_0 + \Lambda_0(t) \} / S_0^*(t) - 1$. When $\pi_0 = 0$, $m(\gamma_0, \beta_0, \pi_0) = -1$, and the above sample size formula is reduced to the standard PH model sample size formula as given in (1).

Let τ_a , τ_f and τ denote the accrual period, follow-up time and total study length, where $\tau = \tau_a + \tau_f$. We assume that the only censoring is due to administrative censoring at time τ , and there is no loss to follow-up or competing risks. Let $g(t)$ denote the probability density function of accrual times, and three (uniform, increasing and decreasing) accrual patterns are considered in the package. The probability density functions $g(t)$ of accrual times and their corresponding survival functions $S_C(t)$ of the censoring times for the uniform, increasing and decreasing accruals are summarized in Table 1.

2.1. Examples under Parametric Assumption

Uniform Accrual and Exponential Distribution—The uniform accrual assumes that patients enter a study at a constant rate $1/\tau_a$. The exponential distribution with rate of λ_0 assumes that patients in the control arm have mean survival time of $1/\lambda_0$ and hazard risk λ_0 , that is $\lambda_0(t) = \lambda_0$, $\Lambda_0(t) = \lambda_0 t$ and $S_0(t) = e^{-\lambda_0 t}$. Plugging the defined survival functions $S_C(t)$ and other information into formula (3), the sample size is calculated as

$$n = \frac{(Z_{\theta} + Z_{\alpha/2})^2 \left(\int_0^{\tau_f} \lambda_0 e^{-\lambda_0 t} dt + \int_{\tau_f}^{\tau_a + \tau_f} \frac{\tau_a + \tau_f - t}{\tau_a} \lambda_0 e^{-\lambda_0 t} dt \right)}{p(1-p) \beta_0^2 (1 - \pi_0) \left\{ \int_0^{\tau_f} m(\gamma_0, \beta_0, \pi_0) \lambda_0 e^{-\lambda_0 t} dt + \int_{\tau_f}^{\tau_a + \tau_f} \frac{\tau_a + \tau_f - t}{\tau_a} m(\gamma_0, \beta_0, \pi_0) \lambda_0 e^{-\lambda_0 t} dt \right\}^2}, \quad (4)$$

where $m(\gamma_0, \beta_0, \pi_0) = \frac{\pi_0(\gamma_0/\beta_0 + \lambda_0 t)}{\pi_0 + (1 - \pi_0)e^{-\lambda_0 t}} - 1$.

Increasing Accrual and Weibull Distribution—The increasing accrual assumes that patients enter a study with the density function of $g(t) = \frac{2k}{\tau_a^k}$. The Weibull distribution with scale parameter λ_0 and shape parameter k is assumed for survival time of uncured patients, which can be written as $\lambda_0(t) = \lambda_0 k (\lambda_0 t)^{k-1}$, $\Lambda_0(t) = (\lambda_0 t)^k$ and $S_0(t) = e^{-(\lambda_0 t)^k}$. Comparing to the exponential assumption, the Weibull distribution allows increasing hazard rate ($k > 1$), constant hazard rate ($k = 1$) and decreasing hazard rate ($0 < k < 1$). The sample size is calculated as

$$n = \frac{(Z_{\theta} + Z_{\alpha/2})^2 \left(\int_0^{\tau_f} \lambda_0 k (\lambda_0 t)^{k-1} e^{-(\lambda_0 t)^k} dt + \int_{\tau_f}^{\tau_a + \tau_f} \frac{(\tau_a + \tau_f - t)^2}{(\tau_a)^2} \lambda_0 k (\lambda_0 t)^{k-1} e^{-(\lambda_0 t)^k} dt \right)}{p(1-p) \beta_0^2 (1 - \pi_0) \left\{ \int_0^{\tau_f} m(\gamma_0, \beta_0, \pi_0) \lambda_0 k (\lambda_0 t)^{k-1} e^{-(\lambda_0 t)^k} dt + \int_{\tau_f}^{\tau_a + \tau_f} \frac{(\tau_a + \tau_f - t)^2}{(\tau_a)^2} m(\gamma_0, \beta_0, \pi_0) \lambda_0 k (\lambda_0 t)^{k-1} e^{-(\lambda_0 t)^k} dt \right\}^2}, \quad (5)$$

where $m(\gamma_0, \beta_0, \pi_0) = \frac{\pi_0(\gamma_0/\beta_0 + \lambda_0 t^k)}{\pi_0 + (1 - \pi_0)e^{-(\lambda_0 t)^k}} - 1$.

2.2. Example Under Nonparametric Estimation of Parameters ($\hat{S}_0(t)$, $\hat{\pi}_0$, $\hat{\gamma}_0$, $\hat{\beta}_0$)

Let $t_{(1)} < t_{(2)} < \dots < t_{(k)}$ be the distinct failure times. If observed/historical data is available, the survival function $S_0(t)$, cure rate π_0 , log odds ratio γ_0 and log hazard ratio β_0 can be estimated from the PH mixture cure model directly, which is implemented into smcure package in R [1]. In this situation, only α , θ , p and accrual pattern need to be specified. The sample size formula for nonparametric estimation is written as

$$n = \frac{(Z_\theta + Z_{\alpha/2})^2 \sum_{i=1}^k \hat{S}_0(t_{(i)}) S_C(t_{(i)})}{p(1-p) \hat{\beta}_0^2 (1 - \hat{\pi}_0) \left\{ \sum_{i=1}^k \hat{S}_0(t_{(i)}) S_C(t_{(i)}) \hat{m}(\hat{\gamma}_0, \hat{\beta}_0, \hat{\pi}_0; t_{(i)}) \right\}^2}, \quad (6)$$

where $\hat{m}(\hat{\gamma}_0, \hat{\beta}_0, \hat{\pi}_0; t_i) = \hat{\pi}_0 \left\{ \hat{\gamma}_0 / \hat{\beta}_0 + \hat{\Lambda}_0(t) \right\} / \hat{S}_0^*(t) = 1$, $\hat{\Lambda}_0(t) = \log(-\hat{S}_0(t))$, $\hat{S}_0^*(t) = \hat{\pi}_0 + (1 - \hat{\pi}_0) \hat{S}_0(t)$.

3. Package Description

The sample size formula (3) under the exponential or Weibull distribution and formula (6) for the nonparametric estimation with different accrual patterns are implemented in the NPHMC package. The NPHMC function can be called using the following syntax:

```
NPHMC <- function(n, power, alpha, accrualtime, followuptime, p,
  accrualdist=c("uniform", "increasing", "decreasing"), hazardratio, oddsratio,
  pi0, survdist=c("exp", "weib"), k, lambda0, data=NULL)
```

The arguments are:

- **n**: the sample size needed for the power calculation.
- **power**: the power needed for sample size calculation. The default power is 80%.
- **alpha**: the level of significance of statistical test. The default alpha is 0.05.
- **accrualtime**: the length of accrual period.
- **followuptime**: the length of follow-up time.
- **p**: the proportion of subjects in the treatment arm. The default p is 0.5.
- **accrualdist**: the accrual pattern. It can be "uniform", "increasing" or "decreasing".
- **hazardratio**: the hazard ratio of uncured patients between two arms, which is defined as $e^{\beta_0} = \lambda_1(t)/\lambda_0(t)$. The value must be greater than 0 and not equal to 1.
- **oddsratio**: the odds ratio of cure rates between two arms, which is equivalent to $e^{\gamma_0} = \frac{\pi_1}{1-\pi_1} / \frac{\pi_0}{1-\pi_0}$. The value should be greater than 0 if there is cured fraction. When it is 0, the model is reduced to the standard proportional hazards model, which means there is no cure rate.
- **pi0**: the cure rate for the control arm, which is between 0 and 1.
- **survdist**: the survival distribution of uncured patients. It can be "exp" or "weib".
- **k**: if survdist = "weib", the shape parameter k needs to be specified. By default k = 1, which refers to the exponential distribution.

- λ_0 : the scale parameter of exponential distribution or Weibull distribution for survival times of uncured patients in the control arm. The density function of Weibull distribution with shape parameter k and scale parameter λ_0 is given by

$$f(t) = \lambda_0 k (\lambda_0 t)^{k-1} \exp\left(-(\lambda_0 t)^k\right), \quad t > 0,$$

and the corresponding survival distribution is $S(t) = \exp(-(\lambda_0 t)^k)$.

- `data`: if observed/historical data is available, the sample size can be calculated based on the nonparametric estimators from the PH mixture cure model by `smcure` package in R. The data must contain three columns with the order of “Time”, “Status” and “X” where “Time” refers to observed time, “Status” refers to censoring indicator (1 = event of interest happens, and 0 = censoring) and “X” refers to arm indicator (1 = treatment and 0 = control). By default, `data = NULL`.

Remarks:

- We can choose “`oddsratio = 1`” if we believe the difference does not exist in the cure fraction. However, we cannot choose “`hazardratio = 1`” ($e^{\beta_0} = 1$) since β_0 is the denominator in the sample size formulae and cannot be 0.
- If the argument “`data`” is not “`NULL`”, the “`hazardratio`” and the “`oddsratio`” will be automatically calculated by NPHMC package based on the output from `smcure` package. If the argument “`data`” is not “`NULL`” and the “`hazardratio`” and “`oddsratio`” are given, it will give warning message “The “`hazardratio`” and “`oddsratio`” are not needed when data is specified.” If the argument “`data`” is “`NULL`”, we have to specify the value of the “`hazardratio`” and the “`oddsratio`”.

Given power (sample size) and significant level of statistical test, the output of sample size (power) calculation is:

If `data = NULL`, the output will display

- PH Mixture Cure Model: n (Power)
- Standard PH Model: n (Power)

When data is specified, the output will first display the estimators from the `smcure` package in R, and then show results from the NPHMC package.

- Estimators from `smcure` package
- PH Mixture Cure Model: n (Power)
- Standard PH Model: n (Power)

4. Simulation

In this section, we conduct a simulation study to investigate the performance of the NPHMC package based on the PH mixture cure model. Two sets of results are reported. One is based on the fully parametric approach, and the other is based on the nonparametric approach.

The following settings are used in the simulation study: (1) an exponential distribution with parameter $\lambda_0 = 1$, and a Weibull distribution with shape parameter $k = 2$ and scale parameter $\lambda_0 = 1$ are assumed for survival distributions of uncured patients; (2) an accrual period of 3 years and a follow-up time of 4 years; (3) an equal allocation $p = 0.5$; (4) a number of 500 observations is generated in each dataset; (5) simulation results are based on 200 replications.

We first compare the parametric estimation approach based on the exponential distribution with the nonparametric estimation approach in Table 2. We fix $\pi_0 = 0.2$, $\lambda_0 = 1$, and then set $\pi_1 = (0.4, 0.45, 0.5)$ and $\lambda_1 = (1/2, 1/2.5, 1/3)$ respectively, which correspond to the values of $\text{oddsratio} = (2.6667, 3.2727, 4)$ and $\text{hazardratio} = (0.5, 0.4, 0.3)$. In Table 3, we consider the Weibull distribution with $k = 2$. The same settings of odds ratio and hazards ratio are used. At the 95% significant level and 80% power, the estimated sample size and its 95% empirical confidence interval are reported in Tables 2 and 3. Both tables show that the results from the nonparametric sample size estimation are quite close to those based on the parametric approach.

5. Examples

The components needed for sample size calculation includes: sample size, power, censoring distribution (accrual time, follow up time, accrual distribution), and components needed in the mixture cure model (hazard ratio e^{β_0} , odds ratio (e^{γ_0} , π_1 , π_0), and survival distribution). In practice, there is two ways to specify the last component: one is parametric way assuming the Weibull (exponential) survival distribution with all parameters specified; the other way is nonparametric way using the preliminary studies to estimate all parameters needed through smcure package. We implement these two options in NPHMC package, and illustrate how to specify the components needed in the next two subsections.

5.1. Parametric Sample Size Estimation

If survival curve in each arm is assumed to follow the exponential distribution or Weibull distribution, besides the specifications of power, alpha, accrualtime, followuptime and p, in order to calculate the sample size based on the PH mixture cure model, the user needs to give `accrualdist`, `survdist`, `k`, `lambda0`, and assumption of relationship between two arms, such as `hazardratio` and `oddsratio`.

For example, a survival trial will follow a uniform accrual with an accrual period of 3 years and a follow-up period of 4 years with equal amount of patients in each arm ($p = 0.5$). The mean life of uncured patients in the control arm will be 2 years and mean life of uncured patients in the treatment arm will be 2.5 years. Assuming both arms follow the exponential distribution, cure rates are $\pi_0 = 0.1$ and $\pi_1 = 0.2$ for the control and treatment arm, we want to calculate the sample size needed to detect a 25% improvement in mean survival time from 2 to 2.5 years. At 95% significance level and 90% power, the estimated sample size can be obtained by the following code:

```
>
NPHMC(power=0.90,alpha=0.05,accrualtime=3,followuptime=4,p=0.5,accrualdist="uniform",
hazardratio=2/2.5,oddsratio=2.25,pi0=0.1,survdist="exp",k=1,lambda0=0.5)
```

The output is:

```
=====
SAMPLE SIZE CALCULATION FOR PH MIXTURE CURE MODEL AND STANDARD PH MODEL
=====
At alpha = 0.05 and power = 0.9 :
PH Mixture Cure Model: n = 429
Standard PH Model: n = 908
```

A sample size of 429 patients will be needed to achieve a power of 90% based on the PH mixture cure model. The sample size from the standard PH model is 908 which is overestimated if there exists a cure rate.

5.2. Nonparametric Sample Size Estimation when Observed/Historical Data is Available

We illustrate the application of NPHMC package by melanoma data from the ECOG phase III clinical trial E1684 [2]. The ECOG trial E1684 was a two-arm phase III clinical trial comparing high dose interferon alpha-2b with an observation arm. The primary endpoint was relapse-free survival (RFS), with RFS defined as the time from randomization until progression of the tumor or death. Note that our intention here is not to re-design the trial but to show the application of the package.

If an observed/historical data is given, the user only needs to specify power, alpha, accrualtime, followuptime, p, accrualdist and data, because the hazard ratio and cure rates can be directly estimated from the available data. Therefore, the sample size can be obtained by the following code:

```
> NPHMC(power=0.80,alpha=0.05,accrualtime=4,followuptime=3,p=0.5,
accrualdist="uniform",data=e1684szdata)
```

The output is:

```
Call:
smcure(formula = Surv(Time, Status) ~ X, cureform = ~Z, data = data, model =
"ph", Var = FALSE)
Cure probability model:
Estimate
(Intercept) 1.2850677
Z -0.5455204
Failure time distribution model:
Estimate
X -0.1643542
=====
SAMPLE SIZE CALCULATION FOR PH MIXTURE CURE MODEL AND STANDARD PH MODEL
=====
At alpha = 0.05 and power = 0.8 :
PH Mixture Cure Model with KM estimators: n = 454
Standard PH Model with KM estimators: n = 251
```

The package first fitted the data using the smcure R package with the treatment as a covariate. The log hazard ratio is estimated as $\hat{\beta}_0 = -0.164$. The coefficients of logistic regression model for cure probability model is 1.285 and -0.5455, which lead to cure rates for the observation arm and interferon arm as $\hat{\pi}_0 = 1 - \frac{e^{1.285}}{1 + e^{1.285}} = 0.2167$ and $\hat{\pi}_1 = 1 - \frac{e^{1.285 - 0.5455}}{1 + e^{1.285 - 0.5455}} = 0.3231$. Note, this calculation has been automatically done in NPHMC package. To achieve a power of 80%, a sample size of 454 is required based on the estimates from the PH mixture cure model, and 251 based on the standard PH model. It seems it will lead to a underpowered trial if there is a cure fraction.

5.3. Power Calculation

In addition to sample size calculation, this package can also provide power analysis for given sample sizes. Continuing the example in section 5.1, the investigator would like to know the power of the sample size of 100, 150, 200, 250, 300, 350, 400, 450, and 500, which can be calculated by

```
> n=seq(100, 500, by=50)
> NPHMC(n=n, alpha=0.05,accrualtime=3,followuptime=4,p=0.5,
accrualdist="uniform",
hazardratio=2/2.5,oddsratio=2.25,pi0=0.1,survdist="exp", k=1,lambda0=0.5)
=====
POWER CALCULATION FOR PH MIXTURE CURE MODEL AND STANDARD PH MODEL
=====
```

With the same setting of alpha, accrualtime, followuptime, p, accrualdist, hazardratio, oddsratio, pi0, survdist, k and lambda0, sample size varying from 100 to 500 with an increment of 50 can lead to a power of 0.35, 0.48, 0.6, 0.7, 0.77, 0.83, 0.88, 0.91 and 0.94 based on the PH mixture cure model, and 0.19, 0.26, 0.33, 0.4, 0.46, 0.52, 0.58, 0.63 and 0.67 based on the standard PH model. We can see that with the increase of sample size, the power will increase. Comparing the results from both models, the power will be underestimated if ignoring the cure fraction in this situation.

Like nonparametric sample size estimation, the power can also be calculated when observed/historical data is available. Continuing the example in section 5.2, the investigator would like to know the power of the sample size of 100, 150, 200, 250, 300, 350, 400, 450, and 500, which can be calculated by

```
> n=seq(100, 500, by=50)
> NPHMC(n=n,alpha=0.05,accrualtime=4,followuptime=3,p=0.5,
accrualdist="uniform",data=e1684szdata)
Call:
smcure(formula = Surv(Time, Status) ~ X, cureform = ~X, data = data, model =
"ph", Var = FALSE)
Cure probability model:
Estimate
(Intercept) 1.2850677
X -0.5455204
Failure time distribution model:
Estimate
X -0.1643542
=====
POWER CALCULATION FOR PH MIXTURE CURE MODEL AND STANDARD PH MODEL
=====
```

With sample size varying from 100 to 500 with an increment of 50, the power are 0.42, 0.58, 0.71, 0.8, 0.87, 0.91, 0.94, 0.96 and 0.98 based on the standard PH model, and 0.26 0.36 0.46 0.55 0.62 0.69 0.75 0.8 and 0.84 based on the PH mixture cure model. Similar relationship between sample size and power can be found here. However, ignoring the cure

fraction will overestimate the power. These two examples show that without considering the cure fraction, we may under or over estimate the power of a study.

6. Conclusions

We develop an R package to estimate the sample size of the PH mixture cure model. Comparing to the existing software, the main advantage of this package is allowing a cure fraction in survival trial. Besides that, this package can allow patients enter study with different patterns and also different hazard patterns for the uncured patients. Therefore, the NPHMC package provides an important and flexible tool in sample size design in survival trial with or without cure fractions.

Acknowledgments

The project is supported by an award to Drs. Jiajia Zhang and Wenbin Lu from the National Cancer Institute (NCI, Award Number R03CA137790). The content is solely the responsibility of the authors and does not necessarily represent the official views of NCI.

References

1. Cai C, Zou Y, Peng Y, Zhang J. An r-package for estimating semiparametric mixture cure models. *Computer Methods and Programs in Biomedicine*. 2012; 13 smcure.
2. Kirkwood J, Strawderman M, Ernsto M, Smith T, Borden E, Blum R. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the eastern cooperative oncology group trial est 1684. *Journal of Clinical Oncology*. 1996; 14(1):7. [PubMed: 8558223]
3. Kuk A, Chen C. A mixture model combining logistic regression with proportional hazards regression. *Biometrika*. 1992
4. Peng Y, Dear KBG. A nonparametric mixture model for cure rate estimation. *Biometrics*. 2000; 56(1):237–243. [PubMed: 10783801]
5. Schoenfeld D. The asymptotic properties of nonparametric tests for comparing survival distributions. *Biometrika*. 1981
6. Schoenfeld D. Sample-size formula for the proportional-hazards regression model. *Biometrics*. 1983
7. Sy J, Taylor J. Estimation in a cox proportional hazards cure model. *Biometrics*. 2000; 56(1):227–236. [PubMed: 10783800]
8. Wang S, Zhang J, Lu W. Sample size calculation for the proportional hazards cure model. *Statistics in medicine*. 2012; 31:3959–3971. [PubMed: 22786805]

1. .

PH Mixture Cure Model: Power = 0.35 0.48 0.6 0.7 0.77 0.83 0.88 0.91 0.94 Standard PH Model: Power = 0.19 0.26 0.33 0.4 0.46 0.52 0.58 0.63 0.67

2. .

PH Mixture Cure Model: Power = 0.26 0.36 0.46 0.55 0.62 0.69 0.75 0.8 0.84 Standard PH Model: Power = 0.42 0.58 0.71 0.8 0.87 0.91 0.94 0.96 0.98

Table 1

Density functions $g(t)$ of accrual times and corresponding survival functions $S_C(t)$ of censoring times.

Accrual	$g(t)$	$S_C(t)$
Uniform	$g(t) = \begin{cases} \frac{1}{\tau_a} & \text{if } 0 < t \leq \tau_a \\ 0 & \text{otherwise} \end{cases}$	$S_C(t) = \begin{cases} 1 & \text{if } t \leq \tau_f \\ \frac{\tau_a + \tau_f - t}{\tau_a} & \text{if } \tau_f < t \leq \tau_a + \tau_f \\ 0 & \text{if } t > \tau_a + \tau_f \end{cases}$
Increasing	$g(t) = \begin{cases} \frac{2t}{\tau_a^2} & \text{if } 0 < t \leq \tau_a \\ 0 & \text{otherwise} \end{cases}$	$S_C(t) = \begin{cases} 1 & \text{if } t \leq \tau_f \\ \frac{(\tau_a + \tau_f - t)^2}{\tau_a^2} & \text{if } \tau_f < t \leq \tau_a + \tau_f \\ 0 & \text{if } t > \tau_a + \tau_f \end{cases}$
Decreasing	$g(t) = \begin{cases} \frac{2(\tau_a - t)}{\tau_a^2} & \text{if } 0 < t \leq \tau_a \\ 0 & \text{otherwise} \end{cases}$	$S_C(t) = \begin{cases} 1 & \text{if } t \leq \tau_f \\ 1 - \frac{(\tau_f - t)^2}{\tau_a^2} & \text{if } \tau_f < t \leq \tau_a + \tau_f \\ 0 & \text{if } t > \tau_a + \tau_f \end{cases}$

Table 2
Comparison of Exponential Parametric Sample Size Estimation with Nonparametric Sample Size Estimation (200 replications)

π_0	π_1	OR	λ_0	π_1	HR	k	Accrual Rate	Parametric Size	Nonparametric Size	95 % Confidence Interval
0.2	0.4	2.667	1	1/2	0.5	1	Uniform	110	119	(78, 184)
							Increasing	108	122	(75, 199)
							decreasing	112	114	(72, 189)
	0.45	3.273					Uniform	88	93	(63, 134)
							Increasing	87	94	(62, 132)
							decreasing	89	95	(62, 143)
	0.5	4.000					Uniform	73	77	(53, 111)
							Increasing	72	77	(54, 107)
							decreasing	73	76	(52, 105)
0.2	0.5	4.000	1	1/2	0.5	1	Uniform	73	77	(53, 111)
							Increasing	72	77	(54, 107)
							decreasing	73	76	(52, 105)
				1/2.5	0.4		Uniform	59	62	(45, 86)
							Increasing	58	61	(46, 81)
							decreasing	59	60	(43, 85)
				1/3	0.3		Uniform	50	51	(37, 74)
							Increasing	49	51	(38, 70)
							decreasing	51	50	(37, 65)

Table 3
Comparison of Weibull Parametric Sample Size Estimation with Nonparametric Sample Size Estimation (200 replications)

π_0	π_1	OR	λ_0	λ_1	HR	k	Accrual Rate	Parametric Size	Nonparametric Size	95 % Confidence Interval
0.2	0.4	2.667	1	0.707	0.5	2	Uniform	115	124	(74, 218)
							Increasing	115	118	(72, 181)
							decreasing	115	123	(76, 205)
	0.45	3.272					Uniform	92	98	(64, 158)
							Increasing	92	97	(66, 145)
							decreasing	92	95	(63, 142)
	0.5	4.000					Uniform	75	76	(54, 106)
							Increasing	75	76	(56, 104)
							decreasing	75	77	(54, 110)
0.2	0.5	4.000	1	0.707	0.5	2	Uniform	75	76	(54, 106)
							Increasing	75	76	(56, 104)
							decreasing	75	77	(54, 110)
				0.632	0.4		Uniform	61	62	(45, 85)
							Increasing	61	61	(43, 84)
							decreasing	61	63	(44, 85)
				0.548	0.3		Uniform	48	50	(37, 66)
							Increasing	48	50	(33, 69)
							decreasing	48	51	(36, 77)