Enhanced Survival Design with S+SeqTrial 3.g

Overview

Under the null hypothesis, statistical information in the proportional hazards model is directly proportional to the number of events. This applies to the logrank test as well, because it corresponds to the score test of a hazard ratio in the PH model.

Sample size calculations in proportional hazards models thus are based on finding N_J, the maximal number of events to be observed at time τ_J when the last of J potential analyses would be performed (so J is the maximum possible number of analyses). Logistically, however, the clinical trialist needs to know A, the number of subjects to accrue.

In order to calculate the number of subjects needed, some assumptions must be made about the underlying distributions of time to event and time to dropout. In S+SeqTrial 3g, we allow exponential, Weibull and user-specified distributions for time to event and time to dropout, as well as piecewise constant models for hazard rates and dropout.

We also allow different choices for the time t_A of patient accrual, the time $t_f = \tau_J - t_A$ of additional follow-up after accrual of the last subject, and the accrual distribution of entry times. In particular, the accrual distribution can be specified as a beta distribution for the entry times (scaled to the the interval $(0, t_A)$), as the number of subjects accrued in each unit of time, or as a user specified function, returning the individual entry times. The scaled beta distribution conveniently allows many accrual scenarios e.g. like slow early accrual followed by faster accrual later in the trial.

In practice the clinical trialist will consider a variety of accrual scenarios along with time to event and time to dropout distribution assumptions. Under each scenario, S+SEQTRIAL calculates the probability that a randomly chosen patient on the study might have an observed event. S+SEQTRIAL provides a command line function seqPHNSubjects to estimate the number of subjects to accrue using this model. This function can also be accessed from the Time Distns. tab of the dialog for the proportional hazards model. Notationally, we consider that the i^{th} patient would have independent entry, event, and dropout times

$$\begin{aligned} E_i &= \text{ Entry time of individual } i \text{ (from start of study)} \\ T_i &= \text{ Time to event for individual } i \text{ (from time of entry)} \\ D_i &= \text{ Time to dropout for individual } i \text{ (from time of entry)} \end{aligned}$$

distributed according to cumulative distribution functions F_E, F_T, and F_D, respectively.

These times are then used to define the potentially censored observations at time τ according to

$$\begin{aligned} \tau &= \text{ Time of analysis (from start of study)} \\ Y_i &= \text{ Observation time for individual } i \text{ (from time of entry)} \\ \delta_i &= \text{ Indicator of event} \end{aligned}$$

$$\begin{aligned} Y_i &= \max\left(\min\left(T_i, D_i, \tau - E_i\right), 0\right) \\ \delta_i &= \mathbf{1}_{[Y_i = T_i]} \end{aligned}$$

We then choose the value of A to satisfy

$$\begin{aligned} &N_J = A \times P\left(\delta_i = 1 | \tau_J, F_E, F_T, F_D\right) \\ &P\left(\delta_i = 1 | \tau_J, F_E, F_T, F_D\right) = P\left([E_i < \tau_J] \,\&\, [T_i < D_i] \,\&\, [T_i < \tau_J - E_i]\right) \end{aligned}$$

In the clinical trial setting, we consider a two sample problem in which we compare the distribution of time to some event across a "treatment" group (denoted group 1) and a "control" group (denoted group 0). We have measurements of times to the event that are potentially right censored. We presume non-informative censoring may arise from two mechanisms: "administrative censoring" that is due to continued survival without an event at the time of data analysis, and "dropout" in which a subject might be lost to follow-up for other reasons at some time prior to an event being observed.
We consider two time scales:

- "calendar time" which is measured from the time the study starts (which is denoted time 0)
- "study time" which is measured for each patient from the time that patient is accrued to the study.

In either case, time is measured in arbitrary units of the user's choosing (e.g., days, weeks, months, years). All references to time are presumed to be in the same units.

Subject Accrual

The maximal number of subjects to be accrued to the study is denoted A. This quantity may be a fixed value specified by the user or computed from other quantities specified by the user. Alternatively, it may be a random variable with a distribution specified directly by the user or a distribution derived from other quantities that are user specified.

Subject accrual will start at calendar time 0 and continue for t_A time units. This quantity may be a fixed value specified by the user or computed from other quantities that are user specified. When specified directly by the user, t_A will most often be an integer. Alternatively, it may be a random variable with a distribution derived from other quantities that are user specified.

The entry time for the i^{th} subject is denoted E_i. The entry times for all individuals are assumed to be totally independent. Note the following relationship:

$$0 \leq E_1 \leq E_2 \leq E_3 \leq \ldots \leq E_A \leq t_A$$

We let a_k denote the number of subjects accrued between calendar times $k-1$ and k. In the most general case, a_k can be a random variable with distributions specified as described below. The user will also have the option of specifying the exact values of the a_k's. For ease of specification, the user may specify fewer than t_A values, in which case the last specified value is carried forward to all future time intervals. Should a user specify more values than necessary, the extra values will be ignored.

We have the following relationships:

$$a_k = \sum_{i=1}^{A} \mathbf{1}_{[k-1<E_i\leq k]}$$
$$A = \sum_{k=1}^{t_A} a_k$$

A user will specify two of t_A, A, and $(a_1, a_2, \ldots, a_{t_A})$, and the third will be computed.

When computing a point prediction of the sample size to be accrued, the distribution of entry times can be characterized in several ways:

- Specification of a parametric conditional distribution for (E_i/t_A) based on a scaled beta distribution having shape parameters $\alpha > 0, \beta > 0$. In this conditional distribution,

$$F_E(ut_A) = P(E_i/t_A \leq u|\alpha, \beta) = \frac{1}{B(\alpha,\beta)} \int_0^u v^{\alpha-1}(1-v)^{\beta-1}dv$$

  for $0 < u < 1$. Note that choosing $\alpha = 1, \beta = 1$ corresponds to uniform accrual between calendar times 0 and t_A.

- Specification of the exact number of subjects $(a_1, a_2, \ldots)$ to be accrued in each unit of time. For ease of specification, the user may specify fewer than t_A values, in which case the last specified value is carried forward to all future time intervals. Should a user specify more values than necessary, the extra values will be ignored. The individual entry times will then have uniform conditional distributions $(E_i|k-1 < E_i \leq k, a_k) \sim \mathcal{U}(k-1, k)$.

- Specification of a function `entry( )` that will generate the individual entry times. The function should take arguments A, t_A, and additional parameters. The values of the individual entry times are given by $E_i = \texttt{entry}(A, t_A, \text{parameters})\texttt{[i]}$.

When computing an interval prediction of the sample size A to be accrued or the time t_A of subject accrual, there are also several methods for specifying the variability in accrual patterns:

- Specification of the mean rate of subject accrual ω and a parametric conditional distribution for (E_i/t_A) based on a beta distribution having parameters shape parameters $\alpha > 0, \beta > 0$. In this setting, a Poisson process $A(t) \sim Poisson(t\omega)$ can be used to allow variability in A or t_A, but not both. The individual entry times will then be computed using the beta distribution, as above.

- Specification of the mean number of subjects $(\omega_1, \omega_2, \ldots)$ to be accrued in each unit of time. For ease of specification, the user may specify fewer than t_A values, in which case the last specified value is carried forward to all future time intervals. Should a user specify more values than necessary, the extra values will be ignored. The number of subjects accrued in each interval will then be randomly sampled according to a Poisson distribution $a_k \sim Poisson(\omega_k)$, and the individual entry times will then have uniform conditional distribution $(E_i|k-1 < Ei \leq k, a_k) \sim \mathcal{U}(k-1, k)$. When this approach is used either A or t_A will be specified, but not both.

- Specification of a function `entry( )` that will generate the individual entry times. The function will take arguments A and t_A, and the value of the individual entry times will be determined by $E_i = \texttt{entry}(A, t_A)\texttt{[i]}$.

Treatment Assignment

Randomization scheme will be specified by an argument ratio signifying that size of treatment groups will be in the ratio `ratio[1]` on the treatment arm to `ratio[2]` on the control arm. (The default value for both `ratio[1]` and `ratio[2]` is 1).

Time to Event Distribution

The event time for the i^{th} subject is denoted T_i. The event times for all individuals are assumed to be totally independent.

The distribution for event times in the control group can be characterized several ways:

- Specification of a parametric Weibull distribution: $T \sim Weibull(p, \lambda_0)$. In this parametric distribution

$$F_T(t) = P(T \le t) = 1 - \exp\left(-\left(\frac{t}{\lambda_0}\right)^p\right)$$
$$F_T^{-1}(u) = \lambda_0\left(-\log(1-u)\right)^{1/p}$$

  The user may specify either the values of the scale parameter `eventScale` $= \lambda_0$ and shape parameter `eventShape` $= p$ (default $p = 1$) or up to two quantiles of the distribution of time to event using arguments `eventQuantiles` and `eventProbs`. In the latter specification, if only one quantile is supplied, an exponential distribution is presumed ($p = 1$). The default value for `eventProbs` is 0.5 (so the median).

- Specification of a constant hazard $(\lambda_1, \lambda_2, \ldots)$ for events in each unit of time. For ease of specification, the user may specify fewer than $t_A + t_f$ values, in which case the last specified value is carried forward to all future time intervals. Should a user specify more values than necessary, the extra values will be ignored. The cumulative distribution function for the event times is then

$$F_T(t) = P(T \le t) = 1 - \exp\left(-\Lambda(t)\right)$$
$$\Lambda(t) = \sum_{k=1}^{\lfloor t \rfloor} \lambda_k + \lambda_{\lceil t \rceil}\left(t - \lfloor t \rfloor\right)$$

- Specification of a function `event( )` that will generate the individual event times. The function will take arguments A, and the value of the individual entry times will be determined by $T_i =$ `event(`A`)[i]`. (Note: A very common situation will be one in which the user wants to resample from a Kaplan-Meier curve derived from an earlier study.)

Time to Dropout Distribution

The dropout time for the i^{th} subject is denoted D_i. The event times for all individuals are assumed to be totally independent.

The distribution for dropout times can be characterized several ways:

- Specification of a parametric Weibull distribution: $D \sim Weibull(p, \gamma_0)$. In this parametric distribution

$$F_D(t) = P(D \le t) = 1 - \exp\left(-\left(\frac{t}{\gamma_0}\right)^p\right)$$
$$F_D^{-1}(u) = \gamma_0\left(-\log(1-u)\right)^{1/p}$$

The user may specify either the values of the scale parameter `dropoutScale` $= \gamma_0$ and shape parameter `dropoutScale` $= p$ (default $p = 1$) or up to two quantiles of the distribution of time to dropout using arguments `dropoutQuantiles` and `dropoutProbs`. In the latter specification, if only one quantile is supplied, an exponential distribution is presumed ($p = 1$). The default value for `dropoutProbs` is 0.5 (so the median).

- Specification of a constant hazard $(\gamma_1, \gamma_2, \ldots)$ for dropouts in each unit of time. For ease of specification, the user may specify fewer than $t_A + t_f$ values, in which case the last specified value is carried forward to all future time intervals. Should a user specify more values than necessary, the extra values will be ignored. The cumulative distribution function for the dropout times is then

$$F_D(t) = P(D \leq t) = 1 - \exp\left(-\Lambda(t)\right)$$
$$\Lambda(t) = \sum_{k=1}^{\lfloor t \rfloor} \gamma_k + \gamma_{\lceil t \rceil}\left(t - \lfloor t \rfloor\right)$$

- Specification of a function `dropout( )` that will generate the individual dropout times. The function will take arguments A, and the value of the individual dropout times will be determined by $D_i =$ `dropout(`A`)[i]`. (Note: A very common situation will be one in which the user wants to resample from a Kaplan-Meier curve derived from an earlier study.)

Some examples using seqPHNSubjects

Examples numbers such as **A8** in this section refer to the `Examples06.ssc` file in the `seqtrial/scripts/` folder in S+SeqTrial. See that file for output abridged here, and for additional examples. **A** examples focus on accrual, **E** on event times, **D** on dropout times, **T** on theta parameters accrual summary printouts, **O** on operating characteristics, and **P** on power.

I'm not sure about P.

Example A8: User provides $A; (a_1, a_2, \ldots)$

You plan for $A = 700$ subjects, with accrual expected to ramp linearly up to 30 subjects per month (time unit) over the first 6 months and remain at 30 subjects per month thereafter: $a_1 = 5, a_2 = 10, \ldots a_6 = 30, a_7 = \ldots = 30$.

- t_A is determined as the number of time units required to achieve the desired sample size A with the given rates per time unit, i.e. such that

$$\sum_{i=1}^{t_A} a_i = A$$

- Cumulative distribution function for entry times:

$$F_E(u) = P(E_i \leq u) = \frac{\sum_{i=1}^{\lfloor u \rfloor} a_i + a_{\lceil u \rceil}(u - \lfloor u \rfloor)}{\sum_{i=1}^{t_A} a_i}$$

- We will compute the accrual time and study time (and the analysis times, $\tau_1, \tau_2, \ldots, \tau_J$) necessary to see the desired number of events; assuming exponential time to event distribution and no dropout.

Summary:

- **Accrual:** Specify `accrualSize, accrualRate`
  `accrualTime, studyTime` are computed
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

```
dsnA8 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
                       P=c(1, 0.5), accrualSize=700,
                       accrualRate=c(5, 10, 15, 20, 25, 30),
                       eventQuantiles=12, seed=0)
dsnA8
```

Output

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                              a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Poisson process
     Number of subjects:     700
     Accrual time      :     25.83333
     Accrual rate      :      5 10 15 20 25 30
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      700          NA       25.83     54.89
       null   1.0        1      700          NA       25.83     48.51

Timing of analyses:

  Theta = 0.7    Scenario  1
```

```
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      16.66      23.56      29.82      38.69      54.89
    N Accrued     424.23     631.49     700.00     700.00     700.00
     N Events     119.04     238.08     357.11     476.15     595.19

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      15.77      22.21      27.88      35.28      48.51
    N Accrued     398.14     591.28     700.00     700.00     700.00
     N Events     119.04     238.08     357.11     476.15     595.19
```

Example A5: User provides $t_A; (a_1, a_2, \ldots)$

You plan for $t_A = 24$ months (time units) for accrual, with accrual expected to ramp linearly up to 30 subjects per month (time unit) over the first 6 months and remain at 30 subjects per month thereafter: $a_1 = 5, a_2 = 10, \ldots a_6 = 30, a_7 = \ldots = 30$.

- A is determined as $A = \sum_{i=1}^{t_A} a_i$.
- Cumulative distribution function for entry times:

$$F_E(u) = P(E_i \leq u) = \frac{\sum_{i=1}^{\lfloor u \rfloor} a_i + a_{\lceil u \rceil}(u - \lfloor u \rfloor)}{\sum_{i=1}^{t_A} a_i}$$

- We will compute the study time t_f (and the analysis times $\tau_1, \tau_2, \ldots, \tau_J$) necessary to see the desired number of events; assuming exponential time to event distribution and no dropout.

Summary:

- **Accrual:** Specify `accrualTime, accrualRate`
  `studyTime is computed`
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

```
dsnA5 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
                       P=c(1, 0.5), accrualTime=24,
                       accrualRate=c(5, 10, 15, 20, 25, 30),
                       eventQuantiles=12, seed=0)
dsnA5
```

Output

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)
```

```
STOPPING BOUNDARIES: Sample Mean scale
                              a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Poisson process
     Number of subjects:     645
     Accrual time      :     24
     Accrual rate      :      5 10 15 20 25 30
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      645          NA          24     68.24
       null   1.0        1      645          NA          24     58.80

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      16.67      23.57      30.67      41.89      68.24
    N Accrued     424.31     632.00     645.00     645.00     645.00
     N Events     119.04     238.08     357.11     476.15     595.19

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      15.78      22.22      28.38      37.62       58.8
    N Accrued     398.84     591.78     645.00     645.00      645.0
     N Events     119.04     238.08     357.11     476.15      595.2
```

Example A2: User provides $A; t_A; \alpha, \beta$

You plan for $A = 700$ subjects, with $t_A = 24$ months (time units) for accrual. You expect a distribution of accrual times that is approximately beta with $\alpha = 10, \beta = 1$ (so accrual rates increase as the study progresses).

- Cumulative distribution function for entry times:

$$F_E(ut_A) = P(E_i/t_A \leq u|\alpha, \beta) = \frac{1}{B(\alpha, \beta)} \int_0^u \left(\frac{v}{t_A}\right)^{\alpha-1} \left(1 - \frac{v}{t_A}\right)^{\beta-1}$$

- We will compute the study time t_f (and the analysis times $\tau_1, \tau_2, \ldots, \tau_J$) necessary to see the desired number of events; assuming exponential time to event distribution and no dropout.

Summary:

- **Accrual:** Specify `accrualSize, accrualTime, aShapeAccr`
  `aShapeAccr=10` is faster accrual late,
  `studyTime` is computed.
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

```
dsnA2 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
P=c(1, 0.5), accrualSize=700, accrualTime=24, aShapeAccr=10,
eventQuantiles=12, seed=0)
dsnA2
```

Output

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                              a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Beta distribution (shape1=10, shape2=1)
     Number of subjects:     700
     Accrual time      :     24
     Accrual rate      :     Unspecified
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      700          NA          24     61.49
       null   1.0        1      700          NA          24     54.78

Timing of analyses:

  Theta = 0.7    Scenario  1
```

```
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      25.71      30.35      36.54      45.44      61.49
    N Accrued     700.00     700.00     700.00     700.00     700.00
     N Events     119.04     238.08     357.11     476.15     595.19

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      25.16      29.15      34.26      41.65      54.78
    N Accrued     700.00     700.00     700.00     700.00     700.00
     N Events     119.04     238.08     357.11     476.15     595.19
```

Example A7: User provides $A; t_A$; `entry()`

You plan for $A = 700$ subjects, with $t_A = 24$ months (time units) for accrual. You have a function `entry()` that returns times according to some distribution that you expect for accrual times.

- Cumulative distribution function for entry times will be approximated using a large sample of accrual times from the user-supplied function `entry()`.
- We will compute the study time t_f (and the analysis times $\tau_1, \tau_2, \ldots, \tau_J$) necessary to see the desired number of events; assuming exponential time to event distribution and no dropout.

Summary:

- **Accrual:** Specify `accrualTime, accrualSize, entry, entryArgs`
  `studyTime` is computed.
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

```
entryA7 <- function(n, time, entryArgs) {
        distn <- entryArgs$distn
        distn <- distn - min(distn)
        distn <- distn / max(distn)
        sample (distn, n, replace=T) * time
}
set.seed(1)
entryArgsA7 <- list(distn=rbeta(1000, 0.5, 0.5))
dsnA7 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, accrualSize=700, entry=entryA7,
        entryArgs=entryArgsA7, eventQuantiles=12, seed=0)
dsnA7
```

Output

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)
```

```
STOPPING BOUNDARIES: Sample Mean scale
                             a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     User-specified function: entryA7
     Number of subjects:     700
     Accrual time      :     24
     Accrual rate      :     Unspecified
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      700          NA          24     53.77
       null   1.0        1      700          NA          24     47.37

Timing of analyses:

  Theta = 0.7    Scenario  1
             Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time       13.6      22.21      28.73       37.6      53.77
    N Accrued      371.2     562.23     700.00      700.0     700.00
     N Events      119.0     238.08     357.11      476.2     595.19

  Theta = 1    Scenario  1
             Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      12.47      20.64       26.8      34.16      47.37
    N Accrued     350.01     519.59      700.0     700.00     700.00
     N Events     119.04     238.08      357.1     476.15     595.19
```

Example: User provides $t_A; \alpha, \beta; \tau_J$

This is similar to example **A2**, except that instead of specifying the total number of accrued we specify the total study time.

You plan for $t_A = 24$ months (time units) for accrual and $\tau_J = 36$ months (time units) total for the study, including the accrual period. You expect a distribution of accrual times that is approximately beta with $\alpha = 10, \beta = 1$ (as for example **A2**)

- We will compute the sample size A so that by time $\tau_J = t_A + t_f$ we expect to have seen the desired number of events.

- We will compute the sample size A so that by time $\tau_J = t_A + t_f$ we expect to have seen the desired number of events. In comparison to example **A2**, where the study time was 61.49 under the alternative hyptohesis, here the study time is much shorter, only 36. This allows less time for followup, and as a result the total accrual must be much larger, 1197 under the alternative hypothesis instead of 700.

Summary:

- **Study time:** Specify `studyTime`
- **Accrual:** Specify `accrualTime`
  uniform accrual (default)
  `accrualSize` is computed
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

```
dsnA <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, aShapeAccr=10, studyTime = 36,
        eventQuantiles=12, seed=0)
dsnA
```

Output

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                                a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Beta distribution (shape1=10, shape2=1)
     Number of subjects:     Unspecified
     Accrual time      :     24
     Accrual rate      :     Unspecified
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1     1197          NA          24        36
```

```
      null   1.0        1     1071          NA          24         36

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      24.02      26.42      29.11      32.22       36.0
    N Accrued    1197.00    1197.00    1197.00    1197.00     1197.0
     N Events     119.04     238.08     357.11     476.15      595.2

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      23.98       26.3      28.98      32.07       36.0
    N Accrued    1062.62     1071.0    1071.00    1071.00     1071.0
     N Events     119.04      238.1     357.11     476.15      595.2
```

Example A14: User provides t_A

You plan for $t_A = 24$ months (time units) accrual, with uniform accrual.

In contrast to the examples above, this example is incompletely specified; various combinations of accrual size and study time will provide the required number of events.

Also, in this example we use graphical procedures to compare accrual plans.

- We will consider a range of accrual sizes A (or equivalently, accrual rates a).
- We will compute the study time t_f and (analysis times $\tau_1, \tau_2, \ldots, \tau_J$) necessary to see the desired number of events; assuming exponential time to event distribution and no dropout.

Summary:

- **Accrual:** Specify accrualTime
  uniform accrual (default)
  range of `accrualSize, studyTime` is computed
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

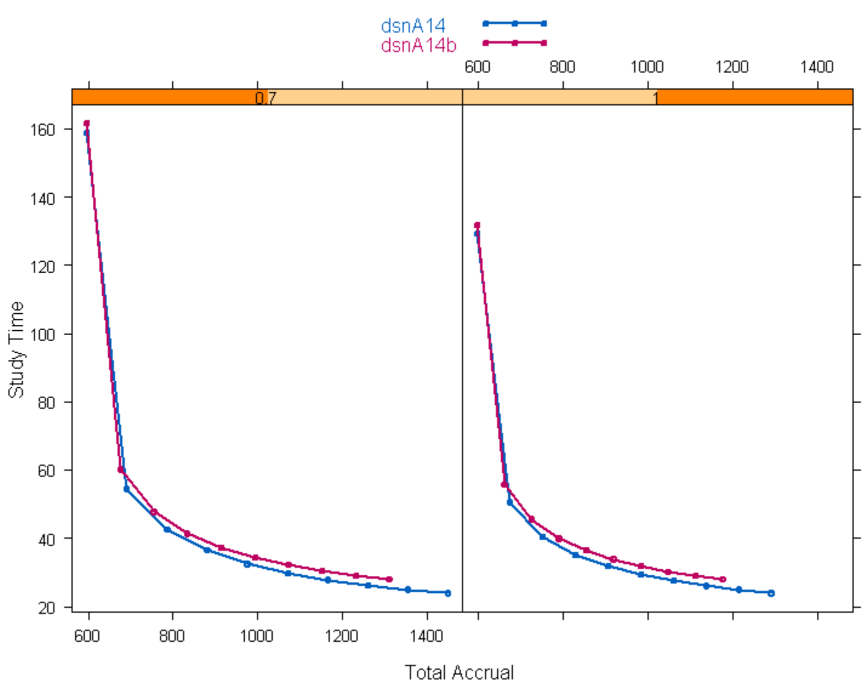
```
dsnA14 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7, P=c(1,0.5),
                        accrualTime=24, eventQuantiles=12, seed=0)
dsnA14

seqPlotAccrualFupTime(dsnA14)

dsnA14b <- update(dsnA14, accrualTime = 28)
seqPlotAccrualFupTime(dsnA14, dsnA14b)

## Test combination of seqDesignExtd and seqDesign
dsnA14d <- seqDesign("hazard", nbr=5, test.type="less", alt=0.7,P=c(1,0.5))
seqPlotAccrualFupTime(dsnA14, dsnA14d)
# Excludes dsnA14d and gives warning (as expected)

seqPlotPHNSubjects(dsnA14)
```

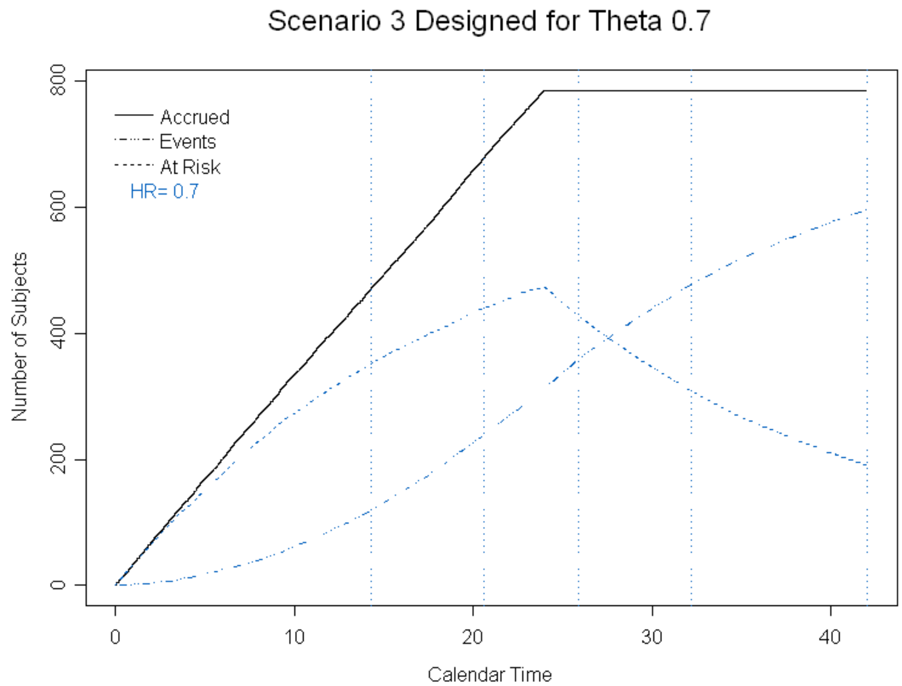
Output (abridged)

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                              a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Uniform distribution
     Number of subjects:     Unspecified
     Accrual time      :     24
     Accrual rate      :     Unspecified
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1    596.0       24.83          24    158.93
alternative   0.7        2    690.8       28.78          24     54.52
alternative   0.7        3    785.6       32.73          24     42.52
alternative   0.7        4    880.3       36.68          24     36.46
alternative   0.7        5    975.1       40.63          24     32.56
alternative   0.7        6   1069.9       44.58          24     29.82
alternative   0.7        7   1164.7       48.53          24     27.83
alternative   0.7        8   1259.4       52.48          24     26.24
alternative   0.7        9   1354.2       56.43          24     25.02
alternative   0.7       10   1449.0       60.38          24     23.99
       null   1.0        1    596.0       24.83          24    129.39
       null   1.0        2    673.2       28.05          24     50.57
...
       null   1.0       10   1291.0       53.79          24     23.99

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      15.76      23.59      31.97      46.53      158.9
    N Accrued     392.82     585.59     596.00     596.00      596.0
     N Events     119.04     238.08     357.11     476.15      595.2
```

```
  Theta = 0.7    Scenario  2
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      14.55      21.59      28.09      37.28      54.52
    N Accrued     420.12     622.37     690.78     690.78     690.78
     N Events     119.04     238.08     357.11     476.15     595.19
...
  Theta = 0.7    Scenario  10
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      9.713      14.16      17.71      20.97      23.99
    N Accrued    587.309     857.79    1073.06    1268.05    1448.29
     N Events    119.038     238.08     357.11     476.15     595.19

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      14.73      22.02       29.1      41.08      129.4
    N Accrued     366.96     547.00      596.0     596.00      596.0
     N Events     119.04     238.08      357.1     476.15      595.2
...
  Theta = 1    Scenario  10
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      9.524      14.05      17.75      21.02      23.99
    N Accrued    512.979     757.91     957.21    1132.08    1290.32
     N Events    119.038     238.08     357.11     476.15     595.19
```

use selected figures here





Example A15: User provides $(a_1, a_2, \ldots)$

You plan for accrual expected to ramp linearly up to 30 subjects per month (time unit) over the first 6 months and remain at 30 subjects per month thereafter: $a_1 = 5, a_2 = 10, \ldots a_6 = 30, a_7 = \ldots = 30$.

This example is incompletely specified; various combinations of accual size (or accrual time) and study time will provide the required number of events.

- We will consider a range of accrual sizes A (or equivalently, total accrual times t_A).
- We will compute the study time t_f and (analysis times $\tau_1, \tau_2, \ldots, \tau_J$) necessary to see the desired number of events; assuming exponential time to event distribution and no dropout.

Summary:

- **Accrual: Specify** `accrualRate`
  range of `accrualSize, studyTime` is computed
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** none (default)

Command-line Code

```
dsnA15 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7, P=c(1,0.5),
                        accrualRate=c(5,10,15,20,25,30), eventQuantiles=12, seed=0)
dsnA15
```

Output (abridged)

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                             a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Poisson process
     Number of subjects:     Unspecified
     Accrual time      :     Unspecified
     Accrual rate      :      5 10 15 20 25 30
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1    596.0          NA       22.37    167.91
alternative   0.7        2    653.0          NA       24.27     74.63
...
alternative   0.7       10   1108.6          NA       39.45     39.47
       null   1.0        1    596.0          NA       22.37    138.66
...
       null   1.0       10   1041.9          NA       37.23     37.34

Timing of analyses:

  Theta = 0.7    Scenario  1
             Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time       22.7      33.18      42.56      56.99      167.9
    N Accrued      326.0     494.98     596.00     596.00      596.0
     N Events      119.0     238.08     357.11     476.15      595.2

  Theta = 0.7    Scenario  2
             Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      21.68      31.47      39.94      50.69      74.63
    N Accrued     339.12     512.53     652.96     652.96     652.96
     N Events     119.04     238.08     357.11     476.15     595.19
...
```

```
  Theta = 0.7    Scenario  10
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      16.62      23.61      29.35      34.56      39.47
    N Accrued     422.29     633.41     806.76     961.94    1108.62
     N Events     119.04     238.08     357.11     476.15     595.19

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      20.61      30.12      38.51      50.44      138.7
    N Accrued     310.54     473.90     596.00     596.00      596.0
     N Events     119.04     238.08     357.11     476.15      595.2
...
  Theta = 1    Scenario  10
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      15.68      22.12      27.65      32.62      37.34
    N Accrued     395.42     588.06     753.71     904.07    1041.93
     N Events     119.04     238.08     357.11     476.15     595.19
```

Examples E1–E5: Specifying Event Distributions

These examples demonstrate different ways to specify event distributions—two ways to specify Weibull distributions, an example with piecewise exponential hazard distributions, an example with a custom event function, and an example using pilot data.

The examples have the same accrual specification — accrual time of 24 months and study time of 60 months, and uniform accrual rate (except accrual and study times are modified for the pilot data example).

- Uniform accrual over 24 months, study time 60 months
- **E1:** specify Weibull distribution using quantiles
- **E2:** specify Weibull distribution using shape parameters
- **E3:** specify piecewise exponential distribution
- **E4:** define a function for event times.
- **E5:** use pilot data (using `eventPilot` as an event function).

Summary:

- **Accrual:** Specify `accrualTime, studyTime`
  entry distribution is Uniform, sample size is computed.
- **Dropout:** none (default)
- **Event E1:** `eventQuantiles = 12, 24, eventProbs = 0.5, 0.75` (Weibull)
- **Event E2:** `eventScale = 0.1 eventShape = 2` (Weibull)
- **Event E3:** `eventHazard = 0.01, 0.02, 0.03, 0.04, 0.10, 0.5, 0.05` (piecewise exponential)
- **Event E4:** user-defined function
- **Event E5:** pilot function

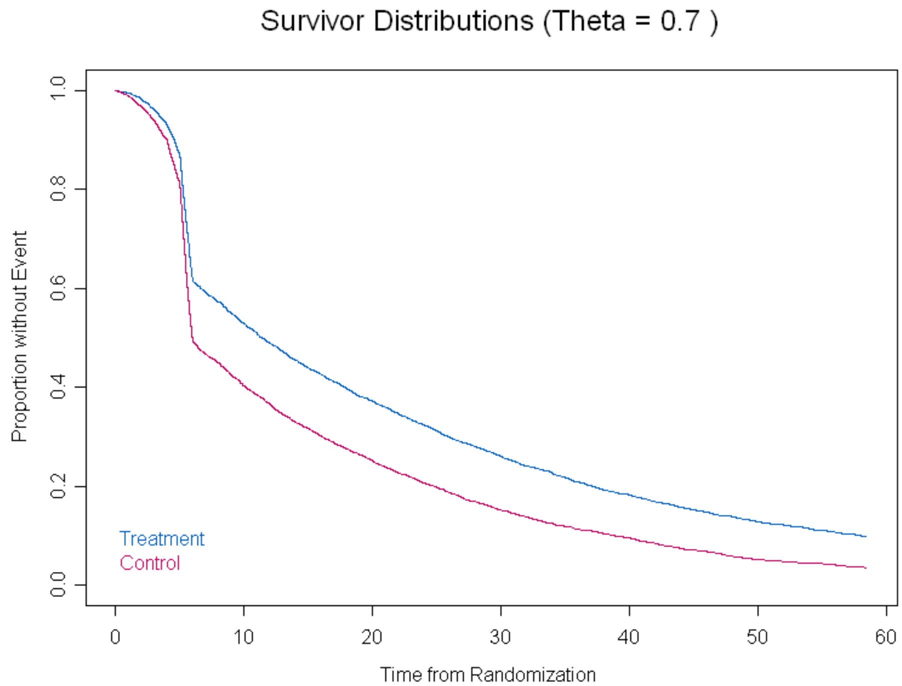
Command-line Code

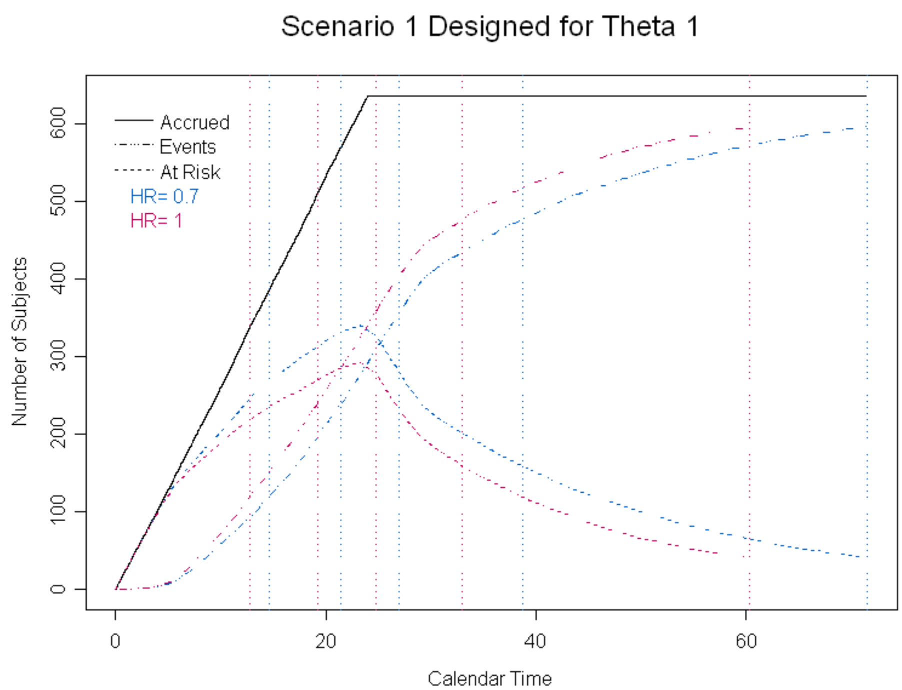
```
dsnE1 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, seed=0,
        eventQuantiles=c(12, 24), eventProbs=c(0.5, 0.75))

dsnE2 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, seed=0,
        eventScale=0.1, eventShape=2)

dsnE3 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, seed=0,
        eventHazard=c(1:4, 10, 50, 5)/100)
seqPlotPHNSubjects(dsnE3, theta=c(0.7,1))

eventE4 <- function(n, nTrt, theta, eventArgs, pcwsHR) {
        distn <- eventArgs$distn
        distn <- sort(distn)
        pdistn.ctrl <- 1-c(0, (1:length(distn)) / length(distn))
        pdistn.treat <- pdistn.ctrl ^ theta
        nctrl <- n - nTrt
        c(as.numeric(distn[cut(runif(nTrt), 1-pdistn.treat)]),
                as.numeric(distn[cut(runif(nctrl), 1-pdistn.ctrl)]))
}
set.seed(1)
eventArgsE4 <- list(distn=rlnorm(1000, 3, 1))
x <- (1:999)/1000
plot(qlnorm(1-x, 3, 1), x, type="l")
lines(qlnorm(1-x, 3, 1), x^0.7)
plot(qlnorm(1-x, 3, 1), x, type="l", xlim=c(0, 60))
lines(qlnorm(1-x, 3, 1), x^0.7)
z <- eventE4(2000, 1000, 0.7, eventArgsE4) # This should be run after
# defining eventArgsE4, to keep the same random numbers as for the
# results below.
plot(survfit(Surv(z, rep(1, 2000))~rep(1:0, each=1000)))
dsnE4 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, event=eventE4,
        eventArgs=eventArgsE4, seed=0)
dsnE4
seqPlotPHNSubjects(dsnE4, theta=c(0.7,1))

# See Examples06.ssc for commands used to create the pilot data set "Lifetest"
plot(survfit(Time ~ Treatment, data = Lifetest))
random <- eventPilot( 190, 100, Lifetest)  # random data
points(sort(random$treatment), 100:1/100, col=2)
points(sort(random$control), 90:1/90, col=3)

dsnE5 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
P=c(1, 0.5), accrualTime=240, studyTime=300, event=eventPilot,
eventArgs=list(data = Lifetest), seed=0)
dsnE5
plot(dsnE5)
```

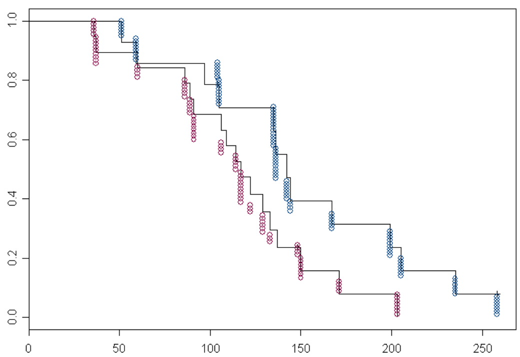
```
seqPlotPHNSubjects(dsnE5)
```

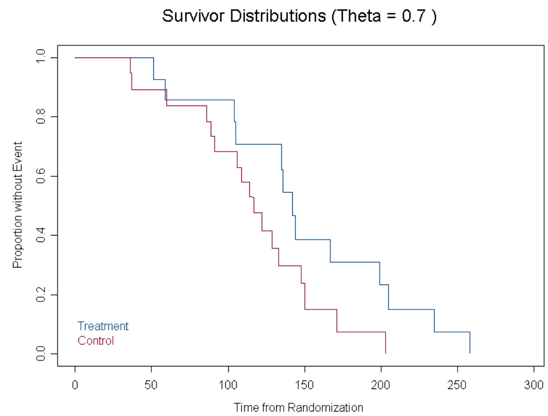
Output Output from example E4 is shown; the others are similar.

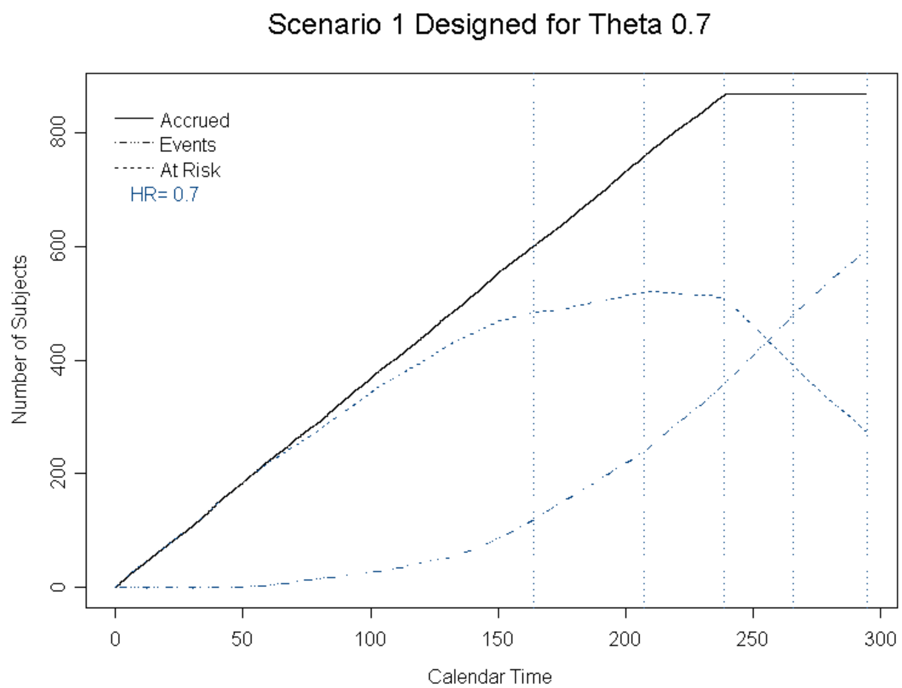
```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                              a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Uniform distribution
     Number of subjects:     Unspecified
     Accrual time      :     24
     Accrual rate      :     Unspecified
  Event distribution:
     User-specified function: eventE4
  Dropout distribution:
     No Dropout

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      796       33.17          24        60
       null   1.0        1      734       30.58          24        60

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      17.91      25.27      32.32      42.32       60.0
    N Accrued     595.65     796.00     796.00     796.00      796.0
     N Events     119.04     238.08     357.11     476.15      595.2

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      17.43      24.64      31.28      41.06       60.0
    N Accrued     534.69     734.00     734.00     734.00      734.0
     N Events     119.04     238.08     357.11     476.15      595.2
```


Survivor Distributions (Theta = 0.7)
Proportion without Event
1.0
0.8
0.6
0.4
0.2
0.0
Treatment
Control
0
10
20
30
40
50
60
Time from Randomization


Scenario 1 Designed for Theta 1
Number of Subjects
600
500
400
300
200
100
0
Accrued
Events
At Risk
HR= 0.7
HR= 1
0
20
40
60
Calendar Time







Examples D1–D6: Specifying Dropout Distributions

These examples demonstrate different ways to specify dropout distributions—exponential or Weibull distributions, piecewise exponential, or using a user-defined function.

The examples have the same accrual specification — accrual time of 24 months and study time of 60 months, and uniform accrual rate. And they share a common event time distribution, exponential with median of 12 months.

- Uniform accrual over 24 months, study time 60 months
- **D1:** specify exponential distribution using median
- **D2:** specify Weibull distribution using quantiles
- **D3:** specify exponential distribution using rate

- **D4:** specify piecewise exponential distribution
- **D5:** specify Weibull distribution using parameters
- **D6:** define a function for event times.

Summary:

- **Accrual:** Specify `accrualTime, studyTime`
  entry distribution is Uniform, sample size is computed.
- **Event:** exponential with median 12
- **Dropout D1:** `dropoutQuantiles = 120` (exponential)
- **Dropout D2:** `dropoutQuantiles = 120, 240, dropoutProbs = 0.5 0.75` (Weibull)
- **Dropout D3:** `dropoutHazard = 1/173.1234` (exponential)
- **Dropout D4:** `dropoutHazard = (1:20)/100` (piecewise exponential)
- **Dropout D5:** `dropoutShape = 1, dropoutScale = 173.1234` (Weibell, exponential)
- **Dropout D6:** user-defined function

Command-line Code

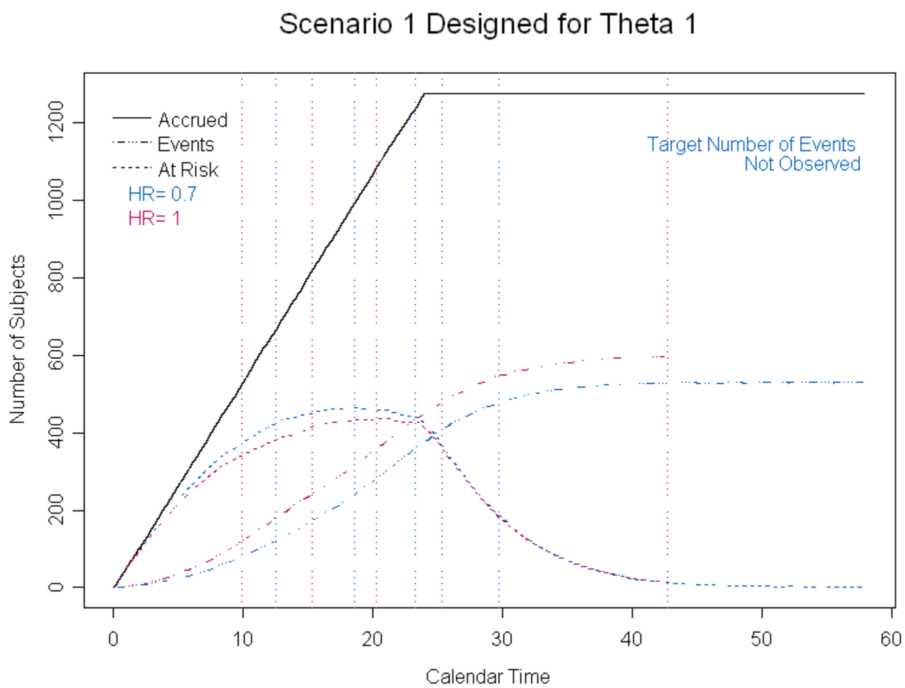
```
dsnD1 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropoutQuantiles=120, seed=0)
seqPlotPHNSubjects(dsnD1,theta=c(0.7,1))

dsnD2 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropoutQuantiles=c(120, 240), dropoutProbs=c(0.5, 0.75),
        seed=0)

dsnD3 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropoutHazard=1/173.1234, seed=0)

dsnD4 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropoutHazard=(1:20)/100, seed=0)
seqPlotPHNSubjects(dsnD4,theta=c(0.7,1))

dsnD5 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropoutShape=1, dropoutScale=173.1234, seed=0)

dropoutD6 <- function (n, dropoutArgs) {
        distn <- dropoutArgs$distn
        distn <- sort(distn)
        pdistn <- 1-c(0, (1:length(distn)) / length(distn))
        as.numeric(distn[cut(runif(n), 1-pdistn)])
```

```
}
set.seed(1)
dropoutArgsD6 <- list(distn=rlnorm(1000, 4, 1))
#descrip(dropoutArgs$distn)
#descrip(dropout(1000, dropoutArgs))
dsnD6 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropout=dropoutD6, dropoutArgs=dropoutArgsD6, seed=0)
seqPlotPHNSubjects(dsnD6,theta=c(0.7,1))
```

Output Output from example D6 is shown; the others are similar.

```
PROBABILITY MODEL and HYPOTHESES:
   Two arm study of censored time to event response variable
   Theta is hazard ratio (Treatment : Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >= 1      (size  = 0.025)
    Alternative hypothesis : Theta <= 0.7    (power = 0.975)

STOPPING BOUNDARIES: Sample Mean scale
                              a      d
    Time 1 (NEv= 119.04) 0.4499 1.0872
    Time 2 (NEv= 238.08) 0.6707 0.9557
    Time 3 (NEv= 357.11) 0.7662 0.9026
    Time 4 (NEv= 476.15) 0.8190 0.8724
    Time 5 (NEv= 595.19) 0.8523 0.8523

ACCRUAL INFORMATION:
  Accrual distribution:
     Uniform distribution
     Number of subjects:     Unspecified
     Accrual time      :     24
     Accrual rate      :     Unspecified
  Event distribution:
     Exponential (hazard=0.05776227; 50th %ile=12)
  Dropout distribution:
     User-specified function: dropoutD6

Accrual summary table:
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      765       31.88          24        60
       null   1.0        1      721       30.04          24        60

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      13.85      20.67      26.74       35.7       60.0
    N Accrued     443.12     660.23     765.00      765.0      765.0
     N Events     119.04     238.08     357.11      476.2      595.2

  Theta = 1    Scenario  1
```

```
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time       13.2      19.99      25.88      34.24       60.0
    N Accrued      398.1     600.51     721.00     721.00      721.0
     N Events      119.0     238.08     357.11     476.15      595.2
```



Example T1: Theta values for printout

This example provides a what to specify theta values (hazard ratios) are used in printouts of the Accrual summary and Timing of analyses tables. Examples A0 and T1 are identical, except for specification of the theta values for printouts.

Command-line Code

```
dsnA0 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualSize=700, accrualTime=24, seed=0,
        eventQuantiles=12)

dsnT1 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualSize=700, accrualTime=24, seed=0,
        eventQuantiles=12, accrTheta=(7:10)/10)

# Equivalent results can be obtained using seqPHNSubjects:
set.seed(0) # Use same random numbers as for dsnT1
seqPHNSubjects(dsnA0, accrTheta = 7:10/10)
```

Output The printout for A0 includes accrual summaries at the null and alternative hypotheses:

```
Accrual summary table:
```

```
            theta Scenario NAccrual accrualRate accrualTime studyTime
alternative   0.7        1      700       29.17          24     52.78
       null   1.0        1      700       29.17          24     46.26

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      14.44      21.42       27.8      36.71      52.78
    N Accrued     422.52     625.70      700.0     700.00     700.00
     N Events     119.04     238.08      357.1     476.15     595.19

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      13.39      20.02      25.67      33.05      46.26
    N Accrued     391.60     584.48     700.00     700.00     700.00
     N Events     119.04     238.08     357.11     476.15     595.19
```

The printout for T1, in contrast, includes the specified theta values:

```
Accrual summary table:
     theta Scenario NAccrual accrualRate accrualTime studyTime
[1,]   0.7        1      700       29.17          24     52.78
[2,]   0.8        1      700       29.17          24     50.12
[3,]   0.9        1      700       29.17          24     48.00
[4,]   1.0        1      700       29.17          24     46.19

Timing of analyses:

  Theta = 0.7    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      14.44      21.42       27.8      36.71      52.78
    N Accrued     422.52     625.70      700.0     700.00     700.00
     N Events     119.04     238.08      357.1     476.15     595.19

  Theta = 0.8    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      14.04      20.96      26.97      35.24      50.12
    N Accrued     410.86     612.07     700.00     700.00     700.00
     N Events     119.04     238.08     357.11     476.15     595.19

  Theta = 0.9    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      13.69      20.47      26.28      34.11       48.0
    N Accrued     400.07     597.52     700.00     700.00      700.0
     N Events     119.04     238.08     357.11     476.15      595.2

  Theta = 1    Scenario  1
              Analysis 1 Analysis 2 Analysis 3 Analysis 4 Analysis 5
Analysis Time      13.41      20.05      25.75       33.1      46.19
    N Accrued     391.46     584.70     700.00      700.0     700.00
     N Events     119.04     238.08     357.11      476.2     595.19
```

Example O2: Simulation-based Operating Characteristics

This example demonstrates the use of simulation-based operating characteristics. The accrual, event, and dropout specifications match earlier examples.

Summary:

- **Accrual:** Specify `accrualTime, studyTime`
  uniform accrual rate, sample size is computer
- **Event:** `eventQuantiles = 12` (median for exponential distribution)
- **Dropout:** exponential with median 120
- **Operating Characteristics:** evaluate 7 alternatives

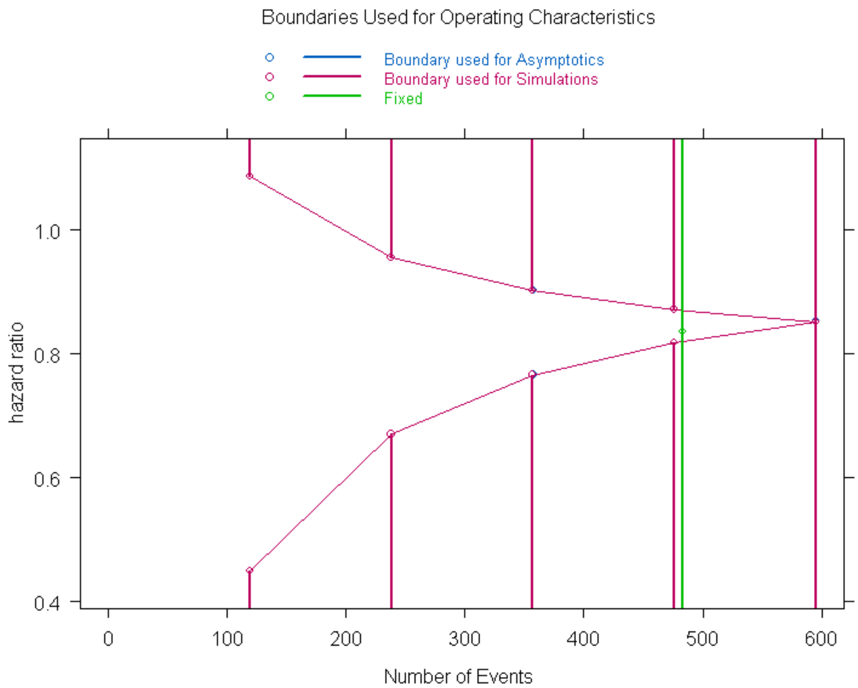
Command-line Code

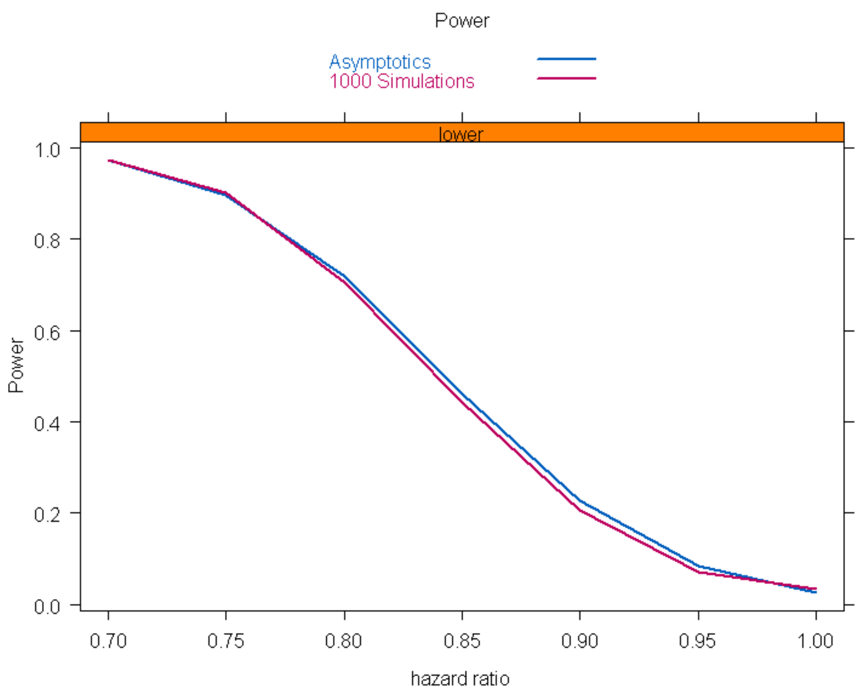
```
dsnO2 <- seqDesignExtd("hazard", nbr=5, test.type="less", alt=0.7,
        P=c(1, 0.5), accrualTime=24, studyTime=60, eventQuantiles=12,
        dropoutQuantiles=120, seed=0)
dsnO2.OC <- seqOperatingCharExtd(dsnO2,
                                 theta=c(1, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7),
                                 Nsimul=1000)
dsnO2.OC
plot(dsnO2.OC)
seqPlotASN(list(AsympOC=dsnO2.OC$AsympOC, SimulOC=dsnO2.OC$SimulOC))
seqPlotPower(list(AsympOC=dsnO2.OC$AsympOC, SimulOC=dsnO2.OC$SimulOC))
seqPlotStopProb(list(AsympOC=dsnO2.OC$AsympOC, SimulOC=dsnO2.OC$SimulOC))
seqPlotInference(dsnO2.OC)
```

Output

```
...
##Asymptotic Operating Characteristics
Operating characteristics
 Theta      ASN Power.lower
  1.00 260.9190      0.0250
  0.95 309.8256      0.0853
  0.90 362.1537      0.2267
  0.85 400.7051      0.4606
  0.80 406.9328      0.7186
  0.75 378.8188      0.8985
  0.70 333.6713      0.9750

Stopping Probabilities:
 Theta Time 1 Time 2 Time 3 Time 4 Time 5
  1.00 0.3241 0.3378 0.1999 0.0987 0.0396
  0.95 0.2309 0.2839 0.2290 0.1642 0.0921
  0.90 0.1513 0.2132 0.2388 0.2349 0.1617
  0.85 0.0899 0.1551 0.2575 0.2938 0.2037
  0.80 0.0480 0.1452 0.3201 0.3138 0.1729
  0.75 0.0241 0.2139 0.4091 0.2615 0.0914
  0.70 0.0161 0.3690 0.4379 0.1497 0.0273
```

```
##Simulated Operating Characteristics ( Nsimul = 1000 )
Operating characteristics
 Theta     ASN Power.lower
  1.00 264.299       0.032
  0.95 305.949       0.071
  0.90 357.952       0.205
  0.85 397.698       0.443
  0.80 403.529       0.705
  0.75 387.940       0.902
  0.70 332.129       0.974

Stopping Probabilities:
 Theta Time 1 Time 2 Time 3 Time 4 Time 5
  1.00  0.326  0.327  0.197  0.100  0.050
  0.95  0.228  0.291  0.246  0.152  0.083
  0.90  0.158  0.209  0.257  0.219  0.157
  0.85  0.094  0.166  0.247  0.290  0.203
  0.80  0.048  0.150  0.326  0.315  0.161
  0.75  0.017  0.186  0.422  0.270  0.105
  0.70  0.015  0.381  0.429  0.148  0.027

Mean Calendar Time at Analyses:
 Theta  Time 1  Time 2  Time 3  Time 4  Time 5
  1.00 13.3074 19.9616 25.7440 33.5963 50.0555
  0.95 13.4726 20.1810 26.0716 34.1821 51.2402
  0.90 13.6268 20.4002 26.3621 34.7055 52.5185
  0.85 13.7625 20.6323 26.7433 35.4564 54.1693
  0.80 13.9154 20.8816 27.1270 36.1008 55.6996
  0.75 14.1209 21.1481 27.5320 36.8940 58.0324
  0.70 14.3639 21.4532 28.0126 37.7999 60.2390

Mean Subjects Accrued at Analyses:
 Theta  Time 1  Time 2  Time 3 Time 4 Time 5
  1.00 402.936 604.307 725.974    726    726
  0.95 407.925 611.034 725.998    726    726
  0.90 412.485 617.586 726.000    726    726
  0.85 416.612 624.338 726.000    726    726
  0.80 420.953 632.228 726.000    726    726
  0.75 428.284 640.210 726.000    726    726
  0.70 434.029 649.157 726.000    726    726
```


Boundaries Used for Operating Characteristics
Boundary used for Asymptotics
Boundary used for Simulations
Fixed
hazard ratio
1.0
0.8
0.6
0.4
0
100
200
300
400
500
600
Number of Events


Power
Asymptotics
1000 Simulations
lower
Power
1.0
0.8
0.6
0.4
0.2
0.0
0.70
0.75
0.80
0.85
0.90
0.95
1.00
hazard ratio