R code
```
> install.packages("BuyseTest", quiet = TRUE)
> library(BuyseTest)
```

R output
```
Loading required package: Rcpp
BuyseTest version 3.1.0
```

R code
```
> set.seed(10)
> data <- simBuyseTest(100, n.strata = 2)
> head(data)
```

R output
```
      id treatment  eventtime status toxicity      score strata
   <num>    <fctr>      <num>  <num>   <fctr>      <num> <fctr>
1:     1         C 0.17392093      1      yes -2.1250686      a
2:     2         C 0.16255166      0      yes  0.5211787      a
3:     3         C 0.08302502      1      yes -0.0464229      b
4:     4         C 0.22204972      0       no -1.1494717      b
5:     5         C 0.11669726      1       no  0.6293383      a
6:     6         C 0.11885540      1      yes -0.7264715      a
```

R code
```
> e.BT <- BuyseTest(treatment ~ tte(eventtime, status = status),
                    data = data)
```

R output
```
         Generalized Pairwise Comparisons

Settings
- 2 groups  : Control = C and Treatment = T
- 1 endpoint:
priority endpoint  type          operator             event
1        eventtime time to event higher is favorable  status (0 1)
- right-censored pairs: probabilistic score based on the survival curves

Point estimation and calculation of the iid decomposition

Estimation of the estimator's distribution
- method: moments of the U-statistic

Gather the results in a S4BuyseTest object
```

R code

```
> summary(e.BT)
```

R output

```
       Generalized pairwise comparisons with 1 endpoint

- statistic       : net treatment benefit  (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- confidence level: 0.95
- inference       : H-projection of order 1 after atanh transformation
- treatment groups: T (treatment) vs. C (control)
- censored pairs  : probabilistic score based on the survival curves
- results
endpoint total(%) favorable(%) unfavorable(%) neutral(%) uninf(%)  Delta CI [2.5% ; 97.
eventtime     100        57.39          42.61          0        0 0.1479  [-0.0293;0.31
```

R code

```
> confint(e.BT, statistic = "winRatio")
```

R output

```
          estimate        se  lower.ci upper.ci null   p.value
eventtime 1.347081 0.2450411 0.9430953 1.924118    1 0.1014458
```

R code

```
> e.BThalf <- BuyseTest(treatment ~ tte(eventtime, status),
                        data = data, add.halfNeutral = TRUE, trace = FALSE)
> model.tables(e.BThalf, statistic = "favorable")
```

R output

```
   endpoint total favorable unfavorable neutral uninf     Delta  lower.ci  upper.ci   p
1 eventtime   100  57.39388    42.60612       0     0 0.5739388 0.4852354 0.6581263 0.1
```

R code

```
> coef(e.BThalf, statistic = "winRatio")
```

R output

```
[1] 1.347081
```

R code

```
> e.MBT <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 1) + bin(toxicity,
                     data = data, trace = 0)
> model.tables(e.MBT)
```

R output

```
   endpoint threshold total favorable unfavorable neutral uninf   delta  Delta lower.ci
1 eventtime     1e+00 100.0      10.2        2.55    87.2     0  0.0768 0.0768 -0.00928
3  toxicity     1e-12  87.2      18.8       24.72    43.7     0 -0.0590 0.0178 -0.13396
```

R code

```
plot(e.MBT)
```

R code

```
plot(e.MBT, type = "racetrack")
```

R code

```
> e.BTindiv <- BuyseTest(treatment ~ tte(eventtime, status = status),
                         data = data, keep.pairScore = TRUE)
> getPairScore(e.BTindiv)
```

R output

```
       index.C index.T favorable unfavorable neutral        uninf weight
    1:       1     101 0.9192694  0.08073064       0 0.000000e+00      1
    2:       2     101 0.5695583  0.43044167       0 1.110223e-16      1
    3:       3     101 1.0000000  0.00000000       0 0.000000e+00      1
    4:       4     101 0.4969601  0.50303994       0 0.000000e+00      1
    5:       5     101 1.0000000  0.00000000       0 0.000000e+00      1
   ---
 9996:      96     200 0.2858328  0.71416716       0 0.000000e+00      1
 9997:      97     200 0.8120919  0.18790807       0 0.000000e+00      1
 9998:      98     200 0.6171644  0.38283561       0 0.000000e+00      1
 9999:      99     200 0.6171644  0.38283561       0 0.000000e+00      1
10000:     100     200 0.4596044  0.54039560       0 0.000000e+00      1
```

R code

```
> eBT.perm <- BuyseTest(treatment ~ cont(score), data = data,
                      method.inference = "varexact permutation")
> model.tables(eBT.perm)
```

R output

```
  endpoint total favorable unfavorable neutral uninf  Delta   p.value
1    score   100     53.67       46.33       0     0 0.0734 0.3698664
```

R code

```
> wilcox.test(score ~ treatment, data = data, correct = FALSE)$p.value
```

R output

```
0.3698664
```

R code
```
> rbind(confint(e.BTindiv, transformation = TRUE),
        confint(e.BTindiv, transformation = FALSE))
```

R output
```
             estimate         se     lower.ci  upper.ci null    p.value
eventtime   0.1478776 0.08897931 -0.02931684 0.3160612    0 0.10150573
eventtime1 0.1478776 0.08897931 -0.02651861 0.3222739    0 0.09652625
```

R code
```
> NTB <- coef(e.BTindiv)
> sigma.NTB <- sqrt(crossprod(getIid(e.BTindiv)))
> sigmaTrans.NTB <- sigma.NTB/(1-NTB^2)
> c(estimate = NTB, se = sigmaTrans.NTB, p.value = 2*(1-pnorm(NTB/sigma.NTB)),
    pTrans.value = 2*(1-pnorm(atanh(NTB)/sigmaTrans.NTB)))
```

R output
```
  estimate          se      p.value pTrans.value
0.14787764   0.09096860   0.09652625   0.10150573
```

R code
```
BuyseTest.options(method.inference = "permutation", n.resampling = 1000,
                  statistic = "winRatio")
```

R code
```
> data("prodige", package = "BuyseTest")
> head(prodige)
```

R output
```
    id treatment     OS statusOS     PFS statusPFS toxicity    sex
<num>    <fctr>  <num>    <num>  <num>     <num>    <num> <fctr>
1:      1          C 0.0349        1 0.0349          0        1      F
2:      2          C 2.2790        0 2.2052          1        4      F
3:      3          C 0.2008        1 0.2008          0        1      M
4:      4          C 0.3418        1 0.3418          0        1      F
```

R code
```
> e.BR <- BuyseTest(treatment ~ tte(OS, statusOS, threshold = 6)
                + cont(toxicity, operator = "<0", threshold = 2)
                + tte(OS, statusOS, threshold = 1)
                + cont(toxicity, operator = "<0"),
                  data = prodige)
> plot(e.BR)
```

R code
```
> summary(e.BR)
```

R code

```
> M.threshold <- cbind(OS_t6 = c(3:5,3:5),
                       toxicity_t2 = c(2,2,2,3,3,3),
                       OS_t2 = 1,
                       toxicity = 0)
> M.threshold
```

R output

```
     OS_t6 toxicity_t2 OS_t2 toxicity
[1,]     3           2     1        0
[2,]     4           2     1        0
[3,]     5           2     1        0
[4,]     3           3     1        0
[5,]     4           3     1        0
[6,]     5           3     1        0
```

R code

```
> eBR.Se <- sensitivity(e.BR, band = TRUE,
                       threshold = M.threshold)
> plot(eBR.Se)
```

R code

```
> e.NTB_Gehan <- BuyseTest(treatment ~ tte(OS, statusOS), scoring.rule = "Gehan",
                          data = prodige, keep.pairScore = TRUE, trace = FALSE)
> getPairScore(e.NTB_Gehan)[1:2,]
```

R output

```
   index.C index.T favorable unfavorable neutral uninf weight
1:       1     403         1           0       0     0      1
2:       2     403         0           0       0     1      1
```

R code

```
> e.NTB_Peron <- BuyseTest(treatment ~ tte(OS, statusOS), scoring.rule = "Peron",
                          data = prodige, keep.pairScore = TRUE, trace = FALSE)
> getPairScore(e.NTB_Peron)[1:2,]
```

R output

```
   index.C index.T favorable unfavorable neutral        uninf weight
1:       1     403 1.0000000     0.00000       0 0.0000000000      1
2:       2     403 0.5286551     0.47068       0 0.0006648516      1
```

R code

```
> e.NTB_Latta <- BuyseTest(treatment ~ tte(OS, statusOS), scoring.rule = "Peron",
                            data = prodige, trace = FALSE,
                            model.tte = prodlim(Hist(OS, statusOS) ~ 1, data = prodige))
```

R code

```
> e.NTB_restricted <- BuyseTest(treatment ~ tte(OS, statusOS, restriction = 24),
                                 scoring.rule = "Peron", data = prodige)
```

R code

```
> simFCT <- function(n.C, n.T){
   out <- rbind(data.frame(Y=stats::rt(n.C, df = 5), group=0),
                data.frame(Y=stats::rt(n.T, df = 5) + 0.5, group=1)
                )
   return(out)
}
> set.seed(10)
> simFCT(2,2)
```

R output

```
            Y group
1  0.02241932     0
2 -1.07273566     0
3  1.26072274     1
4  0.24187644     1
```

R code

```
> e.power <- powerBuyseTest(formula = group ~ cont(Y),
                            sim = simFCT, sample.size = c(10,25,50),
                            n.rep = 100, seed = 10, cpus = 1)
> summary(e.power)
```

R output

```
         Simulation study with Generalized pairwise comparison
with 100 samples

- net benefit statistic (null hypothesis Delta=0)
endpoint threshold n.T n.C mean.estimate sd.estimate mean.se rejection.rate
       Y     1e-12  10  10        0.2258      0.2651  0.2475           0.12
                    25  25        0.2297      0.1455  0.1585           0.23
                    50  50        0.2331      0.1089  0.1118           0.57

n.T          : number of observations in the treatment group
n.C          : number of observations in the control group
mean.estimate: average estimate over simulations
sd.estimate  : standard deviation of the estimate over simulations
mean.se      : average estimated standard error of the estimate over simulations
rejection    : frequency of the rejection of the null hypothesis over simulations
(standard error: H-projection of order 1| p-value: after transformation)
```

R code

```
> e.n <- powerBuyseTest(formula = group ~ cont(Y),
                        sim = simFCT, power = 0.8,
                        n.rep = c(1000,10), seed = 10, trace = 2, cpus = 1)
> summary(e.n)
```

R output

```
       Determination of the sample using a large sample (T=2000, C=2000)

|++++++++++++++++++++++++++++++++++++++++++++++++++| 100% elapsed=06s
- estimated effect (variance): 0.23748050.2612110.241430.24983750.2455650.238980.227548
- estimated sample size      : m=84, n=84

Simulation study with BuyseTest

Simulation
- repetitions: 1000
- cpus       : 1

|++++++++++++++++++++++++++++++++++++++++++++++++++| 100% elapsed=16s
```

R output

```
  Sample size calculation with Generalized pairwise comparison
  for a power of 0.8 and type 1 error rate of 0.05

- estimated sample size (mean [min;max]): 84 [71;96] controls
                                          84 [71;96] treated

- net benefit statistic (null hypothesis Delta=0)
endpoint threshold n.T n.C mean.estimate sd.estimate mean.se rejection.rate
       Y     1e-12  84  84        0.2441      0.0864  0.0859          0.773

n.T          : number of observations in the treatment group
n.C          : number of observations in the control group
mean.estimate: average estimate over simulations
sd.estimate  : standard deviation of the estimate over simulations
mean.se      : average estimated standard error of the estimate over simulations
rejection    : frequency of the rejection of the null hypothesis over simulations
(standard error: H-projection of order 1| p-value: after transformation)
```

$$U - \Delta = \underbrace{\frac{1}{m}\sum_{i=1}^{m} h_E(i)}_{\text{Experimental group}} + \underbrace{\frac{1}{n}\sum_{j=1}^{n} h_C(j)}_{\text{Control group}} + \underbrace{\frac{1}{mn}\sum_{i=1}^{n}\sum_{j=1}^{m} h_{EC}(i,j)}_{\text{Second order term}}$$

where for $i \in \{1, \dots, m\}, h_E(i) = \mathbb{E}[\mathbb{1}_{Y_i^E > Y_j^C} - \mathbb{1}_{Y_j^C > Y_i^E} \mid Y_i^E] - \Delta$

$j \in \{1, \dots, n\}, h_C(j) = \mathbb{E}[\mathbb{1}_{Y_i^E > Y_j^C} - \mathbb{1}_{Y_j^C > Y_i^E} \mid Y_j^C] - \Delta$

$$\widehat{\sigma}_U \underbrace{\approx}_{\text{First order}} \frac{1}{m^2}\sum_{i=1}^{m} h_E^2(i) + \frac{1}{n^2}\sum_{j=1}^{n} h_C^2(j)$$

$$p^{\mathcal{P}} = \frac{1}{1+P}\left\{1 + \sum_{p=1}^{P} \mathbb{1}_{\left|\Delta^{\mathcal{P}(p)}\right| \geq |\Delta|}\right\}$$

$$\mathbb{P}\left[Y_i^E > Y_j^C | \widetilde{Y}_i^E, \Omega_i^E, \widetilde{Y}_j^C, \Omega_j^C\right] = \left\{ \begin{array}{c} 0.75 \text{ for } i = i_1 \\ 1 \text{ for } i = i_2 \end{array} \right.$$

$$\left(\widetilde{Y}_{i_1}^E, \widetilde{Y}_{i_2}^E, \widetilde{Y}_j^C, \Omega_{i_1}^E, \Omega_{i_2}^E, \Omega_j^C\right) = (4.7, 6.1, 1.5, 1, 1, 0)$$

$$U_{ij} = \mathbb{P}\left[Y_i > Y_j + \tau | \widetilde{y}_i, \omega_i, \widetilde{y}_j, \omega_j\right] - \mathbb{P}\left[Y_j > Y_i + \tau | \widetilde{y}_i, \omega_i, \widetilde{y}_j, \omega_j\right]$$

(ω_i, ω_j)	$\tilde{y}_i - \tilde{y}_j \leq -\tau$	$\lvert\tilde{y}_i - \tilde{y}_j\rvert < \tau$	$\tilde{y}_i - \tilde{y}_j \geq \tau$
(1, 1)	-1	0	1
(0, 1)	$\frac{S(\tilde{y}_j+\tau)+S(\tilde{y}_j-\tau)}{S(\tilde{y}_i)} - 1$	$\frac{S(\tilde{y}_j+\tau)}{S(\tilde{y}_i)}$	1
(1, 0)	-1	$-\frac{S(\tilde{y}_i+\tau)}{S(\tilde{y}_j)}$	$1 - \frac{S(\tilde{y}_i+\tau)+S(\tilde{y}_i-\tau)}{S(\tilde{y}_j)}$
(0, 0)	$\dots$	$\frac{\int_{\tilde{y}_i}^{\infty} S(t+\tau)dS(t) - \int_{\tilde{y}_j}^{\infty} S(t+\tau)dS(t)}{S(\tilde{y}_i)S(\tilde{y}_j)}$	$\dots$

$$\mathbb{P}\left[Y^E > Y^C\right] - \mathbb{P}\left[Y^C > Y^E\right]$$

$$\mathbb{P}\left[Y^E > Y^C\right] + 0.5\mathbb{P}\left[Y^E = Y^C\right]$$

$$\frac{\mathbb{P}\left[Y^E > Y^C\right] + 0.5\mathbb{P}\left[Y^E = Y^C\right]}{\mathbb{P}\left[Y^C > Y^E\right] + 0.5\mathbb{P}\left[Y^C = Y^E\right]}$$

$$\frac{\mathbb{P}\left[Y^E > Y^C\right]}{\mathbb{P}\left[Y^C > Y^E\right]}$$

$$\begin{aligned}
\delta_1 =& \mathbb{P}\left[Y_1^E > Y_1^C + \tau_1\right] - \mathbb{P}\left[Y_1^C > Y_1^E + \tau_1\right] \\
\delta_2 =& \mathbb{P}\left[Y_2^E > Y_2^C \middle| |Y_1^E - Y_1^C| \leq \tau_1\right] - \mathbb{P}\left[Y_2^C > Y_2^E \middle| |Y_1^E - Y_1^C| \leq \tau_1\right]
\end{aligned}$$

$$\begin{aligned}
\Delta_1 &= \delta_1 \\
\Delta_2 &= \delta_1 + \delta_2
\end{aligned}$$

$$\boxed{\begin{aligned}
\Delta_1 &= \delta_1 \\
\Delta_2 &= \delta_1 + \delta_2
\end{aligned}}$$

$$\boxed{\begin{aligned}
\delta_1 =& \mathbb{P}\left[Y_1^E > Y_1^C + \tau_1\right] - \mathbb{P}\left[Y_1^C > Y_1^E + \tau_1\right] \\
\delta_2 =& \mathbb{P}\left[Y_2^E > Y_2^C \middle| |Y_1^E - Y_1^C| \leq \tau_1\right] - \mathbb{P}\left[Y_2^C > Y_2^E \middle| |Y_1^E - Y_1^C| \leq \tau_1\right]
\end{aligned}}$$