

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% ; 97.5%] p.value
eventtime    100      57.39      42.61      0      0 0.1479 [-0.0293;0.3161] 0.10151
```

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.value
1 eventtime 100 57.39388 42.60612 0 0 0.5739388 0.4852354 0.6581263 0.1019135
```

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, operator = "<0"
                        data = data, trace = 0)
> model.tables(e.MBT)
```

R output

	endpoint	threshold	total	favorable	unfavorable	neutral	uninf	delta	Delta	lower.ci	upper.ci	p.val
1	eventtime	1e+00	100.0	10.2	2.55	87.2	0	0.0768	0.0768	-0.00928	0.162	0.08
3	toxicity	1e-12	87.2	18.8	24.72	43.7	0	-0.0590	0.0178	-0.13396	0.169	0.81

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(getLid(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 = prodlm(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){
  df.C <- data.frame(id = paste0("C",1:n.C), group = 0,
    tox = sample(1:6, n.C, replace=TRUE,
      prob = c(16.09, 15.42, 33.26, 26.18, 8.38, 0.67)/100),
    time = rweibull(n.C, scale = 9.995655, shape = 1.28993),
    event = 1)
  df.T <- data.frame(id = paste0("T",1:n.T), group = 1,
    tox = sample(1:6, n.T, replace=TRUE,
      prob = c(8.21, 13.09, 31.29, 30.87, 12.05, 4.49)/100),
    time = rweibull(n.T, scale = 13.16543, shape = 1.575269),
    event = 1)
  return(rbind(df.C,df.T))
}
> set.seed(10)
> simFCT(2,2)
```

R output

```
id group tox      time event
1 C1      0  4  8.821945      1
2 C2      0  3  4.591318      1
3 T1      1  3 15.495787      1
4 T2      1  3 15.557655      1
```

R code

```
> e.power <- powerBuyseTest(group ~ tte(time,event,threshold = 1) + cont(tox, operator = "<0"),
  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
  tox      1e-12  10  10      0.2156      0.2656  0.2468      0.13
                25  25      0.2032      0.1677  0.1582      0.2
                50  50      0.2015      0.1228  0.1121      0.43

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(group ~ tte(time,event, threshold = 1) + cont(tox, operator = "<0"),
                        sim = simFCT, power = 0.8,
                        n.rep = c(1000,10), seed = 10, trace = 2, cpus = 1)
> summary(e.n)
```

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]): 126 [91;155] controls
126 [91;155] treated
```

```
- net benefit statistic (null hypothesis Delta=0)
```

endpoint	threshold	n.T	n.C	mean.estimate	sd.estimate	mean.se	rejection.rate
tox	1e-12	126	126	0.2049	0.069	0.0707	0.818

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)

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

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

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

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

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

$$\mathbb{P} \left[\textcolor{brown}{Y}_i^E > \textcolor{blue}{Y}_j^C \mid \widetilde{Y}_i^E, \Omega_i^E, \widetilde{Y}_j^C, \Omega_j^C \right] = \begin{cases} 0.75 & \text{for } i = i_1 \\ 1 & \text{for } i = i_2 \end{cases}$$

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

$$U_{ij} = \mathbb{P}[\textcolor{brown}{Y}_i > \textcolor{blue}{Y}_j + \tau \mid \widetilde{y}_i, \omega_i, \widetilde{y}_j, \omega_j] - \mathbb{P}[\textcolor{blue}{Y}_j > \textcolor{brown}{Y}_i + \tau \mid \widetilde{y}_i, \omega_i, \widetilde{y}_j, \omega_j]$$

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

$$\mathbb{P}[\textcolor{brown}{Y}^E > \textcolor{blue}{Y}^C] - \mathbb{P}[\textcolor{blue}{Y}^C > \textcolor{brown}{Y}^E]$$

$$\mathbb{P}[\textcolor{brown}{Y}^E > \textcolor{blue}{Y}^C] + 0.5\mathbb{P}[\textcolor{brown}{Y}^E = \textcolor{blue}{Y}^C]$$

$$\frac{\mathbb{P}[\textcolor{brown}{Y}^E > \textcolor{blue}{Y}^C] + 0.5\mathbb{P}[\textcolor{brown}{Y}^E = \textcolor{blue}{Y}^C]}{\mathbb{P}[\textcolor{blue}{Y}^C > \textcolor{brown}{Y}^E] + 0.5\mathbb{P}[\textcolor{blue}{Y}^C = \textcolor{brown}{Y}^E]}$$

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

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

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

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

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