

Overview of the package **BuyseTest**

Brice Ozenne

June 29, 2023

This vignette describes the main functionalities of the **BuyseTest** package. This package implements the Generalized Pairwise Comparisons (GPC) as defined in [Buyse \(2010\)](#) for complete observations, and extended in [Péron et al. \(2018\)](#) to deal with right-censoring. When considering a single endpoint, the GPC procedure can be summarized as follow. Denote the endpoint by Y in the treatment group and by X in the control group. Given a threshold of clinical relevance τ , the aim of GPC is to estimate the proportion in favor of treatment $\mathbb{P}[Y \geq X + \tau]$ and the proportion in favor of control $\mathbb{P}[X \geq Y + \tau]$. Other statistics such as the net benefit $\mathbb{P}[Y \geq X + \tau] - \mathbb{P}[X \geq Y + \tau]$ or the win ratio $\frac{\mathbb{P}[Y \geq X + \tau]}{\mathbb{P}[X \geq Y + \tau]}$ can then be deduced. The vignette is written for readers familiar with the GPC framework ¹, e.g. prioritized endpoints, pair, net benefit, win ratio, threshold of clinical relevance, ..., since it focuses on the software aspect of the **BuyseTest** package (not on the underlying statistical model).

The **BuyseTest** package contains three main functions:

- the function **BuyseTest** performs the GPC procedure and is the main function of the package. The user can interact with its output via various methods:
 - **summary** to obtain an overview of the results, including the estimated net benefit. The result table at the end of the output can be directly access using **model.tables**.
 - **coef** to extract the estimates.
 - **confint** to extract estimates, confidence intervals, and p.values.
 - **plot** for a graphical display of the scoring of the pair per endpoint.
 - **sensitivity** to perform a sensitivity analysis on the choice of the threshold(s).
 - **getIid** to extract the iid decomposition of the estimator.
 - **getPairScore** to extract the contribution of each pair to the net benefit/win ratio.
 - **getSurvival** to extract the estimates of the survival used for right-censored endpoints.
 - **BuyseMultComp** to adjust p-values and confidence intervals for multiple comparisons.
- the **powerBuyseTest** function performs simulation studies, e.g. to estimate the statistical power or assess the bias / type 1 error rate of a test for a specific design. The **simBuyseTest** function can facilitate the definition of the data generating mechanism.
- the **BuyseTest.options** function enables the user to access the default values used in the **BuyseTest** package. The function can also change the default values to better match the user needs.

¹if not, [Buyse \(2010\)](#) is a good place to start.

Before going further we need to load the **BuyseTest** package in the R session:

```
library(BuyseTest)
library(data.table)
```

To illustrate the functionalities of the package, we will use the **veteran** dataset from the **survival** package:

```
data(cancer, package = "survival")
head(veteran)
```

```
   trt celltype time status karno diagtime age prior
1    1 squamous  72      1    60        7  69     0
2    1 squamous 411      1    70        5  64    10
3    1 squamous 228      1    60        3  38     0
4    1 squamous 126      1    60        9  63    10
5    1 squamous 118      1    70       11  65    10
6    1 squamous  10      1    20        5  49     0
```

See `?veteran` for a presentation of the database.

Note: the **BuyseTest** package is under active development. Newer package versions may include additional functionalities and fix previous bugs. The version of the package that is being is:

```
utils::packageVersion("BuyseTest")
```

```
[1] '3.0.0'
```

For completeness, the details of the R session used to generate this document are:

```
sessionInfo()
```

```
R version 4.2.0 (2022-04-22)
```

```
Platform: x86_64-pc-linux-gnu (64-bit)
```

```
Running under: Ubuntu 20.04.4 LTS
```

```
Matrix products: default
```

```
BLAS:      /usr/lib/x86_64-linux-gnu/blas/libblas.so.3.9.0
```

```
LAPACK:    /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.9.0
```

```
locale:
```

```
[1] LC_CTYPE=en_US.UTF-8      LC_NUMERIC=C              LC_TIME=en_US.UTF-8
[4] LC_COLLATE=en_US.UTF-8    LC_MONETARY=en_US.UTF-8   LC_MESSAGES=en_US.UTF-8
[7] LC_PAPER=en_US.UTF-8      LC_NAME=C                 LC_ADDRESS=C
[10] LC_TELEPHONE=C           LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
```

```
attached base packages:
```

```
[1] stats      graphics  grDevices  utils      datasets  methods    base
```

other attached packages:

[1] data.table_1.14.2	BuyseTest_3.0.0	Rcpp_1.0.9	prodlim_2019.11.13
[5] ggplot2_3.4.0	survival_3.5-0		

loaded via a namespace (and not attached):

[1] pillar_1.8.1	compiler_4.2.0	tools_4.2.0	digest_0.6.31
[5] lifecycle_1.0.3	tibble_3.1.8	gtable_0.3.1	lattice_0.20-45
[9] pkgconfig_2.0.3	rlang_1.0.6	Matrix_1.4-1	DBI_1.1.3
[13] cli_3.5.0	parallel_4.2.0	SparseM_1.81	withr_2.5.0
[17] dplyr_1.0.10	MatrixModels_0.5-0	generics_0.1.3	vctrs_0.5.1
[21] globals_0.16.1	stats4_4.2.0	grid_4.2.0	tidyselect_1.2.0
[25] glue_1.6.2	listenv_0.8.0	R6_2.5.1	future.apply_1.9.1
[29] fansi_1.0.3	parallelly_1.32.1	lava_1.7.2	magrittr_2.0.3
[33] scales_1.2.1	codetools_0.2-18	splines_4.2.0	assertthat_0.2.1
[37] future_1.28.0	colorspace_2.0-3	utf8_1.2.2	munsell_0.5.0

1 Performing generalized pairwise comparisons (GPC) using the `BuyseTest` function

To perform generalized pairwise comparisons, the `BuyseTest` function needs:

- where the data are stored - argument `data`
- the name of the endpoints - argument `endpoint`
- the type of each endpoint - argument `type`
- the variable defining the two treatment groups - argument `treatment`

The `BuyseTest` function has many optional arguments to specify for example:

- the threshold of clinical relevance associated to each endpoint - argument `threshold`
- the censoring associated to each endpoint (for time to event endpoints) - argument `status`

There are two equivalent ways to define the GPC:

- using a separate argument for each element:

```
BT <- BuyseTest(data = veteran,
                endpoint = "time",
                type = "timeToEvent",
                treatment = "trt",
                status = "status",
                threshold = 20)
```

Generalized Pairwise Comparisons

Settings

- 2 groups : Control = 1 and Treatment = 2
- 1 endpoint:

priority	endpoint	type	operator	threshold	event
1	time	time to event	higher is favorable	20	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

- or via a formula interface. In the formula interface endpoint are wrapped by parentheses. The parentheses must be preceded by their type:
 - binary (**b**, **bin**, or **binary**)
 - continuous (**c**, **cont**, or **continuous**)
 - time to event (**t**, **tte**, or **timetoevent**)

Here we also set the argument `trace` to `FALSE` to execute silently the function:

```
BT.f <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
  data = veteran, trace = FALSE)
```

We can check that the two approaches are equivalent:

```
BT.f@call <- list(); BT@call <- list();
testthat::expect_equal(BT.f, BT)
```

1.1 Displaying the results

The results of the GPC can be displayed using the `summary` method:

```
summary(BT)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net 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: 2 (treatment) vs. 1 (control)
- censored pairs : probabilistic score based on the survival curves
- results
endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) Delta
  time      20      100      37.78      46.54      15.68      0 -0.0877
CI [2.5% ; 97.5%] p.value
[-0.2735;0.1045] 0.37162
```

To display the number of pairs instead of the percentage of pairs that are favorable/unfavorable/neutral/uninformative, set the argument `percentage` to `FALSE`. The `model.tables` method returns the table displayed at the end of the `summary` in a `data.frame` format:

```
model.tables(BT, percentage = FALSE)
```

```
endpoint threshold total favorable unfavorable neutral uninf      Delta  lower.ci
1    time      20  4692  1772.593    2183.886 735.5205      0 -0.08765836 -0.2735301
  upper.ci p.value
1 0.1045245 0.371617
```

An even more concise output can be obtained via the `confint` method:

```
confint(BT)
```

```
              estimate          se  lower.ci  upper.ci null  p.value
time_t20 -0.08765836 0.09760901 -0.2735301 0.1045245    0 0.371617
```

or `coef` method:

```
coef(BT)
```

```
time_t20
-0.08765836
```

By default `summary` displays results relative to the net benefit. To get results for the win ratio set the argument `statistic` to "winRatio":

```
summary(BT, statistic = "winRatio")
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : win ratio (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 1
- confidence level: 0.95
- inference       : H-projection of order 1 after log transformation
- treatment groups: 2 (treatment) vs. 1 (control)
- censored pairs  : probabilistic score based on the survival curves
- results
endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) Delta
time      20      100      37.78      46.54      15.68      0 0.8117
CI [2.5% ; 97.5%] p.value
[0.5134;1.2833] 0.37195
```

See `help(S4BuyseTest-summary)` for more details about the `summary` method and its output.

1.2 Stratified GPC

GPC can be performed for subgroups of a categorical variable - argument `strata`
For instance, the celltype may have huge influence on the survival time and the investigator would like to only compare patients that have the same celltype. In the formula interface this is achieved by adding a single variable in the right hand side of the formula:

```
ffstrata <- trt ~ tte(time, threshold = 20, status = "status") + celltype
BTstrata <- BuyseTest(ffstrata, data = veteran, trace = 0)
```

Not being wrapped by `bin`, `cont` or `tte` differentiates it from endpoint variables. When doing a stratified analysis, the summary method displays strata-specific and global results²:

```
summary(BTstrata, type.display = c("endpoint", "threshold", "strata",
                                   "total", "favorable", "unfavorable", "delta", "Delta"))
```

Generalized pairwise comparisons with 1 endpoint and 4 strata

```
- statistic      : net 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: 2 (treatment) vs. 1 (control)
- strata weights  : 26.38%, 34.63%, 18.47%, 20.52%
- censored pairs  : probabilistic score based on the survival curves
- uninformative pairs: no contribution
- results
```

endpoint	threshold	strata	total(%)	favorable(%)	unfavorable(%)	delta	Delta
time	20	global	100.00	36.70	46.66	-0.0997	-0.0997
		squamous	25.38	14.33	8.77	0.2193	
		smallcell	45.69	12.69	20.88	-0.1792	
		adeno	13.71	4.74	6.15	-0.1034	
		large	15.23	4.30	9.97	-0.3722	

Note that here the numbers in the total/favorable/unfavorable/ columns are relative to the overall sample while the delta is only relative to the strata. The global delta is a sum of the strata specific delta weighted by the empirical proportion of pairs for each strata. The weight of each strata is by default proportional to the number of pairs. This behavior can be changed with the argument `pool.strata`:

```
BTstrataCMH <- BuyseTest(ffstrata, data = veteran, trace = 0, pool.strata = "CMH")
summary(BTstrataCMH, type.display = c("endpoint", "threshold", "strata",
                                       "total", "favorable", "unfavorable", "delta", "Delta"))
```

Generalized pairwise comparisons with 1 endpoint and 4 strata

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
```

²the strata-specific results can be removed by setting the argument `strata` to "global" when calling `summary`.

```

- confidence level: 0.95
- inference      : H-projection of order 1 after atanh transformation
- treatment groups: 2 (treatment) vs. 1 (control)
- strata weights  : 26.38%, 34.63%, 18.47%, 20.52%
- censored pairs  : probabilistic score based on the survival curves
- uninformative pairs: no contribution
- results
endpoint threshold    strata total(%) favorable(%) unfavorable(%)  delta  Delta
time      20      global   100.00          36.70          46.66 -0.0997 -0.0997
              squamous    25.38          14.33           8.77  0.2193
              smallcell    45.69          12.69          20.88 -0.1792
              adeno       13.71           4.74           6.15 -0.1034
              large       15.23           4.30           9.97 -0.3722

```

CMH stands for Cochran-Mantel-Haenszel whose weighted scheme has been advocated in the literature (Dong et al., 2018). We can retrieve the weights by evaluating the number of individual per strata and treatment group:

```

nStrata <- table(veteran$celltype, veteran$strtr)
nStrata

```

```

      1  2
squamous 15 20
smallcell 30 18
adeno     9 18
large     15 12

```

```

nPairStrata <- nStrata[,1]*nStrata[,2]
wStrata <- rbind(default = nPairStrata,
                  CMH = nPairStrata/rowSums(nStrata))
round(100*wStrata/rowSums(wStrata),2)

```

```

      squamous smallcell adeno large
default    25.38     45.69 13.71 15.23
CMH        26.38     34.63 18.47 20.52

```

It is also possible to output strata specific results:

```

confint(BTstrata, stratified = TRUE)

```

```

      estimate      se  lower.ci  upper.ci null  p.value
time_t20.squamous  0.2193074 0.1911515 -0.1690137 0.5486919  0 0.2669352
time_t20.smallcell -0.1792181 0.1540933 -0.4567640 0.1301230  0 0.2551275
time_t20.adeno     -0.1033951 0.2465197 -0.5314450 0.3667172  0 0.6771002
time_t20.large     -0.3722222 0.2190018 -0.7110335 0.1068610  0 0.1240457

```


1.3 Using multiple endpoints

More than one endpoint can be considered by indicating a vector of endpoints, types, and thresholds. In the formula interface, the different endpoints must be separated with a "+" on the right hand side of the formula:

```
ff2 <- trt ~ tte(time, threshold = 20, status = "status") + cont(karno, threshold = 0)
BT.H <- BuyseTest(ff2, data = veteran, trace = 0)
summary(BT.H)
```

Generalized pairwise comparisons with 2 prioritized endpoints

```
- statistic      : net 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: 2 (treatment) vs. 1 (control)
- censored pairs : probabilistic score based on the survival curves
- neutral pairs  : re-analyzed using lower priority endpoints
- results
```

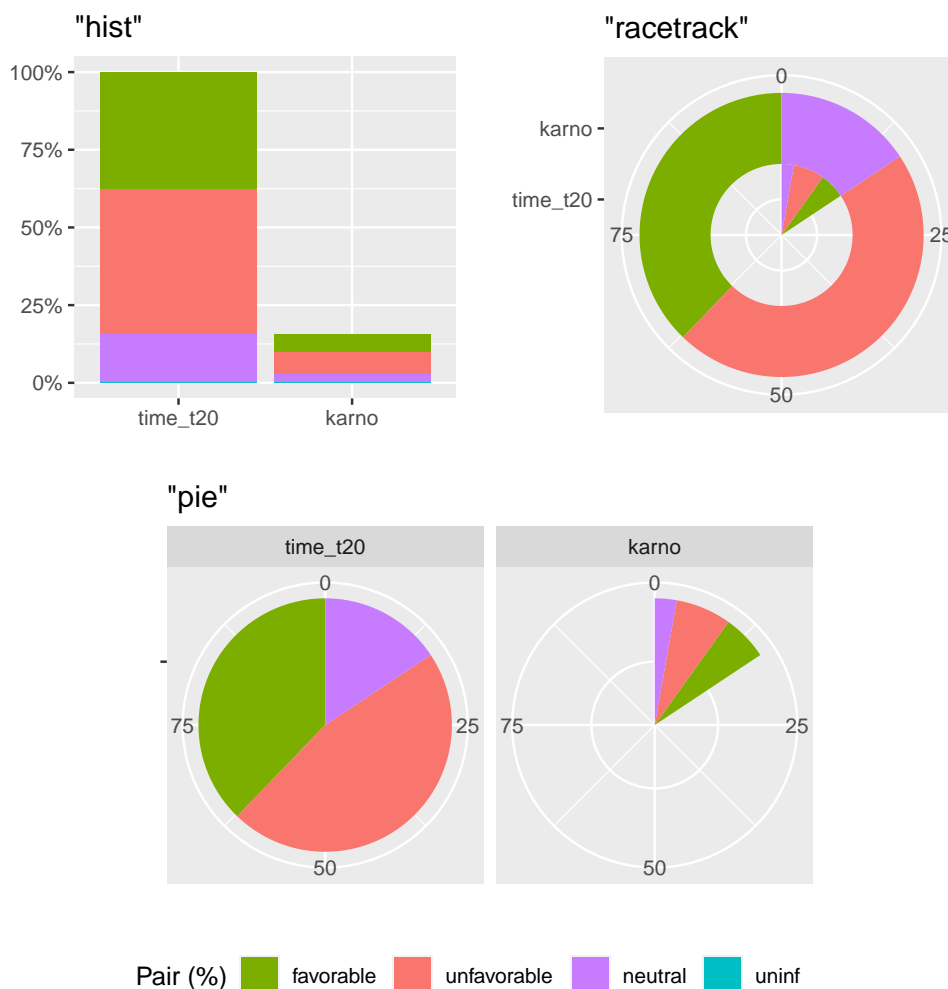
endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	delta	Delta
time	20	100.00	37.78	46.54	15.68	0	-0.0877	-0.0877
karno		15.68	5.78	7.11	2.78	0	-0.0133	-0.1009

```
CI [2.5% ; 97.5%] p.value
[-0.2735;0.1045] 0.37162
[-0.2901;0.0959] 0.31478
```

The hierarchy of the endpoint is defined from left (most important endpoint, here `time`) to right (least important endpoint, here `karno`). In the `summary` output, the confidence intervals and p-values are computed for the column `Delta`, i.e. here -8.77% is the net benefit for the first endpoint (line 1) and -10.09% is the net benefit for the first and second endpoint (line 2). In other words, the last confidence interval and p-value is the one for the analysis over all endpoints (generally the one to report).

A graphical representation of the GPC procedure can be obtained by the `plot` method. It will display the percentage of favorable, unfavorable, neutral, and uninformative pairs per endpoint. Three (equivalent) graphical display are possible, the first one ("`hist`") being the recommended one:

```
plot(BT.H, type = "hist")
plot(BT.H, type = "pie")
plot(BT.H, type = "racetrack")
```



It is also possible to perform the comparisons on all pairs for all endpoints by setting the argument `hierarchical` to `FALSE`:

```
BT.nH <- BuyseTest(ff2, hierarchical = FALSE, data = veteran, trace = 0)
summary(BT.nH)
```

Generalized pairwise comparisons with 2 endpoints

```
- statistic      : net 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: 2 (treatment) vs. 1 (control)
- censored pairs : probabilistic score based on the survival curves
- results
```

endpoint	threshold	weight	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	delta
time	20	0.5	100	37.78	46.54	15.68	0	-0.0877
karno	0.5	100	41.82	44.95	13.24	0	-0.0313	

```
Delta CI [2.5% ; 97.5%] p.value
-0.0438 [-0.1388;0.0519] 0.36977
-0.0595 [-0.2267;0.1111] 0.49514
```

In that case the score of a pair is the weighted sum of the score relative to each endpoint. By default, the weights are all set to the same value but this behavior can be changed by setting the argument `weight` when calling `BuyseTest`, e.g.:

```
ff2w <- trt ~ tte(time, threshold = 20, status = "status", weight = 0.8)
ff2w <- update.formula(ff2w, . ~ . + cont(karno, threshold = 0, weight = 0.2))
BT.nHw <- BuyseTest(ff2w, hierarchical = FALSE, data = veteran, trace = 0)
model.tables(BT.nHw)
```

	endpoint	threshold	weight	total	favorable	unfavorable	neutral	uninf	delta
1	time	2e+01	0.8	100	37.77905	46.54489	15.67606	0	-0.08765836
3	karno	1e-12	0.2	100	41.81586	44.94885	13.23529	0	-0.03132992

	Delta	lower.ci	upper.ci	p.value
1	-0.07012668	-0.2203714	0.08336855	0.3707289
3	-0.07639267	-0.2503756	0.10237001	0.4026905

This has been referred as the O'Brien test in the literature ([Verbeeck et al. \(2019\)](#), section 3.2). Alternatively, one may be interested in the endpoint specific results. This can be performed apply the `BuyseTest` function separately to each endpoint, e.g.:

```
confint(BuyseTest(trt ~ cont(karno, threshold = 0), data = veteran, trace = 0))
```

	estimate	se	lower.ci	upper.ci	null	p.value
karno	-0.03132992	0.09787113	-0.2197111	0.1593037	0	0.7490407

or setting the argument `cumulative` to `FALSE` when calling the `confint` function:

```
confint(BT.nHw, cumulative = FALSE)
```

	estimate	se	lower.ci	upper.ci	null	p.value
time_t20	-0.08765836	0.09760901	-0.2735301	0.1045245	0	0.3716170
karno	-0.03132992	0.09787113	-0.2197111	0.1593037	0	0.7490407

1.4 What if smaller is better?

By default `BuyseTest` will always assume that higher values of an endpoint are favorable. This behavior can be changed by specifying `operator = "<0"` for an endpoint:

```
ffop <- trt ~ tte(time, status = "status", threshold = 20, operator = "<0")
BTinv <- BuyseTest(ffop, data = veteran, trace = 0)
summary(BTinv)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net 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: 2 (treatment) vs. 1 (control)
- censored pairs  : probabilistic score based on the survival curves
- results
endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) Delta
      time      20      100      46.54      37.78      15.68      0 0.0877
CI [2.5% ; 97.5%] p.value
  [-0.1045;0.2735] 0.37162
```

Internally `BuyseTest` will compute the favorable and unfavorable score as usual and then switch them around if the operator equals `"<0"`.

1.5 Stopping comparison for neutral pairs

In presence of neutral pairs, `BuyseTest` will, by default, continue the comparison on the endpoints with lower priority. For instance let consider a dataset with one observation in each treatment arm:

```
dt.sim <- data.table(Id = 1:2,
                    treatment = c("Yes","No"),
                    tumor = c("Yes","Yes"),
                    size = c(15,20))

dt.sim
```

```
   Id treatment tumor size
1:  1      Yes  Yes   15
2:  2      No   Yes   20
```

If we use the GPC with tumor as the first endpoint and size as the second endpoint:

```
BT.pair <- BuyseTest(treatment ~ bin(tumor) + cont(size, operator = "<0"), data = dt.sim,
                    trace = 0, method.inference = "none")
summary(BT.pair)
```

Generalized pairwise comparisons with 2 prioritized endpoints

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- treatment groups: Yes (treatment) vs. No (control)
- neutral pairs   : re-analyzed using lower priority endpoints
- results
endpoint total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) delta Delta
tumor      100           0           0          100         0      0      0
size       100          100           0           0         0      1      1
```

the outcome of the comparison is neutral for the first priority, but favorable for the second. Setting the argument `neutral.as.uninf` to `FALSE` will stop the comparison when a pair is classified as neutral:

```
BT.pair2 <- BuyseTest(treatment ~ bin(tumor) + cont(size, operator = "<0"), data = dt.sim,
                     trace = 0, method.inference = "none", neutral.as.uninf = FALSE)
summary(BT.pair2)
```

Generalized pairwise comparisons with 2 prioritized endpoints

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- treatment groups: Yes (treatment) vs. No (control)
- neutral pairs   : ignored at lower priority endpoints
- results
endpoint total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) delta Delta
tumor      100           0           0          100         0      0      0
size         0           0           0           0         0      0      0
```

So in this case no pair is analyzed at second priority.

1.6 What about p-value and confidence intervals?

Several methods are available in `BuyseTest` to perform statistical inference:

- **permutation test** setting the argument `method.inference` to "permutation". Assuming exchangeability under the null hypothesis, this approach gives valid p-values (regardless to the sample size) for testing the absence of a difference between the groups.

```
BT.perm <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
                    data = veteran, trace = 0, method.inference = "permutation",
                    seed = 10)
summary(BT.perm)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- confidence level: 0.95
- inference      : permutation test with 1000 samples
                   p-value computed using the permutation distribution
- treatment groups: 2 (treatment) vs. 1 (control)
- censored pairs  : probabilistic score based on the survival curves
- results
endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%)  Delta p.value
time          20      100      37.78      46.54      15.68      0 -0.0877 0.36663
```

- **bootstrap resampling** setting the argument `method.inference` to "bootstrap". In large enough samples, this approach gives valid p-values and confidence intervals.

```
BT.boot <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
                    data = veteran, trace = 0, method.inference = "bootstrap",
                    seed = 10)
summary(BT.boot)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- confidence level: 0.95
- inference      : bootstrap resampling with 1000 samples
                   CI computed using the percentile method; p-value by test inversion
- treatment groups: 2 (treatment) vs. 1 (control)
- censored pairs  : probabilistic score based on the survival curves
- results
endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%)  Delta
time          20      100      37.78      46.54      15.68      0 -0.0877
CI [2.5% ; 97.5%] p.value
[-0.2797;0.1108] 0.36364
```

- **asymptotic distribution** setting the argument `method.inference` to "u-statistic". In large enough samples, this approach gives valid p-values and confidence intervals (Ozenne et al., 2021).

```
BT.ustat <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
                     data = veteran, trace = 0, method.inference = "u-statistic")
summary(BT.ustat)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net 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: 2 (treatment) vs. 1 (control)
- censored pairs : probabilistic score based on the survival curves
- results
```

endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	Delta
time	20	100	37.78	46.54	15.68	0	-0.0877

```
CI [2.5% ; 97.5%] p.value
[-0.2735;0.1045] 0.37162
```

The first two approaches require simulating a large number of samples and applying the GPC to each of these samples. The number of samples is set using the argument `n.resampling` and it should large enough to limit the Monte Carlo error when estimating the p-value. Typically should be at least 10000 to get, roughly, 2-digit precision, as exemplified below:

```
set.seed(10)
sapply(1:10, function(i){mean(rbinom(1e4, size = 1, prob = 0.05))})
```

```
[1] 0.0511 0.0491 0.0489 0.0454 0.0516 0.0522 0.0468 0.0483 0.0491 0.0508
```

Indeed, here we get a reasonable approximation of 0.05 (if we round and only keep 2 digits). Note that to get 3 digits precision we would need more samples. The last method does not rely on resampling but on the computation of the influence function of the estimator. Fortunately, when using the Gehan's scoring rule, this does not really involve any extra-calculations and this is therefore very fast to perform. When using the Peron's scoring rule, more serious extra-calculations are involved so the computation time is expected to increase by a factor 5 to 10 compared to the point estimate alone (i.e. `method.inference` equal to "none").

Note: it is possible to relax the exchangeability assumption using a studentized permutation and a bootstrap with better small samples properties using a studentized bootstrap. Both rely on the asymptotic approach to estimate standard errors and are more numerically intensive.

1.7 Is multiple testing a concern with GPC?

Yes, as with any other statistical method. Having a pre-defined statistical plan (i.e. written before looking at the data) specifying the hierarchy of endpoints, their threshold of clinical relevance is recommended.

This being said, there are mainly two way to conclude about results from running multiple GPC:

- **intersection union principle:** one rejects the (global) null hypothesis if there is evidence for an effect in all the GPC analyses. No multiplicity adjustment is needed other than considering the largest p-value among all tests. This is typically a sensitivity analysis: checking that the results are not too sensitive to the choice of an hyperparameter. Consider for instance checking whether the estimated net benefit is similar across a range of threshold of clinical relevance:

```
BTse <- sensitivity(BT.ustat, threshold = seq(0,500, length.out=10),
                    trace = FALSE)

BTse
```

	time	estimate	se	lower.ci	upper.ci	null	p.value
1	0.00000	-0.08752774	0.10041203	-0.27851884	0.11012263	0	0.3858177
2	55.55556	-0.08095829	0.08957699	-0.25229456	0.09530004	0	0.3682107
3	111.11111	-0.03170177	0.07463991	-0.17629003	0.11422560	0	0.6712414
4	166.66667	0.01896964	0.06452954	-0.10713643	0.14447503	0	0.7688360
5	222.22222	0.03315614	0.05523512	-0.07506821	0.14060850	0	0.5486177
6	277.77778	0.04217485	0.04654025	-0.04914025	0.13279075	0	0.3653982
7	333.33333	0.04112991	0.03946828	-0.03631838	0.11808708	0	0.2979105
8	388.88889	0.04075638	0.03300933	-0.02402114	0.10519310	0	0.2174545
9	444.44444	0.04097871	0.03027888	-0.01844156	0.10011054	0	0.1764199
10	500.00000	0.03517173	0.02769280	-0.01915553	0.08929191	0	0.2044340

- **union intersection principle:** one rejects the (global) null hypothesis if there is evidence for an effect for at least one of the GPC analyses.

Adjustment for multiple comparison can be performed via the `BuyseMultComp` function:

```
BuyseMultComp(BT.nHw, cumulative = FALSE, endpoint = 1:2)
```

```
- Univariate tests:
      estimate      se  lower.ci  upper.ci null  p.value lower.band upper.band
1 -0.08765836 0.09760901 -0.2735301 0.1045245  0 0.3716170 -0.2953329 0.1279261
2 -0.03132992 0.09787113 -0.2197111 0.1593037  0 0.7490407 -0.2420777 0.1822409
adj.p.value
1 0.5597555
2 0.9236602
```

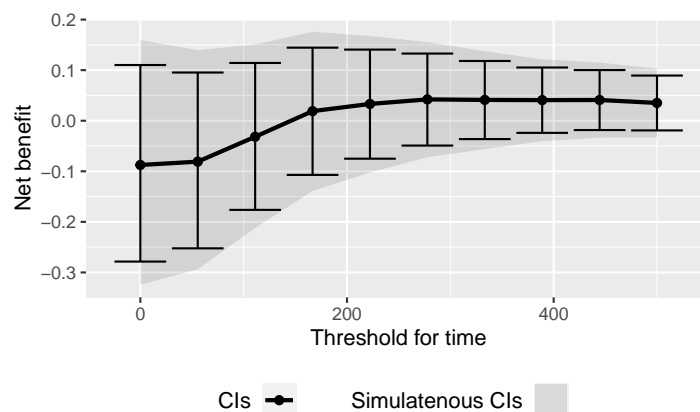
The choice of the threshold of clinical relevance is somehow subjective and it is recommended to see how the results vary as a function of the threshold. This can be easily performed using the `sensitivity` method:


```
BTse.ustat <- sensitivity(BT.ustat, threshold = seq(0,500, length.out=10),
                          band = TRUE, trace = FALSE)
BTse.ustat[,c("time", "estimate", "se", "lower.ci", "upper.ci", "null", "lower.band", "upper.band")]
```

	time	estimate	se	lower.ci	upper.ci	null	lower.band	upper.band
1	0.00000	-0.08752774	0.10041203	-0.27851884	0.11012263	0	-0.32429035	0.1595547
2	55.55556	-0.08095829	0.08957699	-0.25229456	0.09530004	0	-0.29381483	0.1395482
3	111.11111	-0.03170177	0.07463991	-0.17629003	0.11422560	0	-0.21206740	0.1507525
4	166.66667	0.01896964	0.06452954	-0.10713643	0.14447503	0	-0.13877437	0.1757749
5	222.22222	0.03315614	0.05523512	-0.07506821	0.14060850	0	-0.10236938	0.1674732
6	277.77778	0.04217485	0.04654025	-0.04914025	0.13279075	0	-0.07225703	0.1555108
7	333.33333	0.04112991	0.03946828	-0.03631838	0.11808708	0	-0.05595163	0.1374410
8	388.88889	0.04075638	0.03300933	-0.02402114	0.10519310	0	-0.04045901	0.1214368
9	444.44444	0.04097871	0.03027888	-0.01844156	0.10011054	0	-0.03352555	0.1150301
10	500.00000	0.03517173	0.02769280	-0.01915553	0.08929191	0	-0.03294511	0.1029633

Here by setting the argument `band` to `TRUE`, we obtain confidence intervals and p-values adjusted for multiple comparisons. Said otherwise, the columns `lower.ci` and `upper.ci` provide a (pointwise) confidence interval with 95% coverage for a given threshold while the columns `lower.band` and `upper.band` provide a (simultaneous) confidence interval with 95% coverage across all given thresholds. In particular if is interested in the largest effect, the simultaneous confidence interval should be reported instead of the pointwise. They can be displayed using the `autoplot` method:

```
library(ggplot2)
autoplot(BTse.ustat)
```



With multiple endpoints, the thresholds can be specified using a list:

```
BTse.H <- sensitivity(BT.H, trace = FALSE,
                     threshold = list(time = seq(0,500,length = 10), karno = c(0,40,80)))
head(BTse.H)
```

	time	karno	estimate	se	lower.ci	upper.ci	null	p.value
1	0.00000	0	-0.08754474	0.10044847	-0.2786016	0.11017738	0	0.3858987
2	55.55556	0	-0.11177487	0.09915501	-0.2995661	0.08435417	0	0.2636263

```

3 111.11111 0 -0.08618872 0.09822940 -0.2732475 0.10715096 0 0.3826244
4 166.66667 0 -0.05180121 0.09818252 -0.2400240 0.14017526 0 0.5984319
5 222.22222 0 -0.03668720 0.09810141 -0.2253052 0.15458146 0 0.7086747
6 277.77778 0 -0.02906324 0.09773146 -0.2172647 0.16122161 0 0.7663054

```

or a matrix:

```

grid <- expand.grid(list("time_t20" = seq(0,500,length = 10), "karno" = c(0,40,80)))
cbind(head(grid)," " = " ... ",tail(grid))
BTse.H2 <-sensitivity(BT.H, threshold = grid, trace = FALSE)
range(BTse.H-BTse.H2)

```

```

      time_t20 karno      time_t20 karno
1    0.00000    0 ...    222.2222    80
2  55.55556    0 ...    277.7778    80
3 111.11111    0 ...    333.3333    80
4 166.66667    0 ...    388.8889    80
5 222.22222    0 ...    444.4444    80
6 277.77778    0 ...    500.0000    80
[1] 0 0

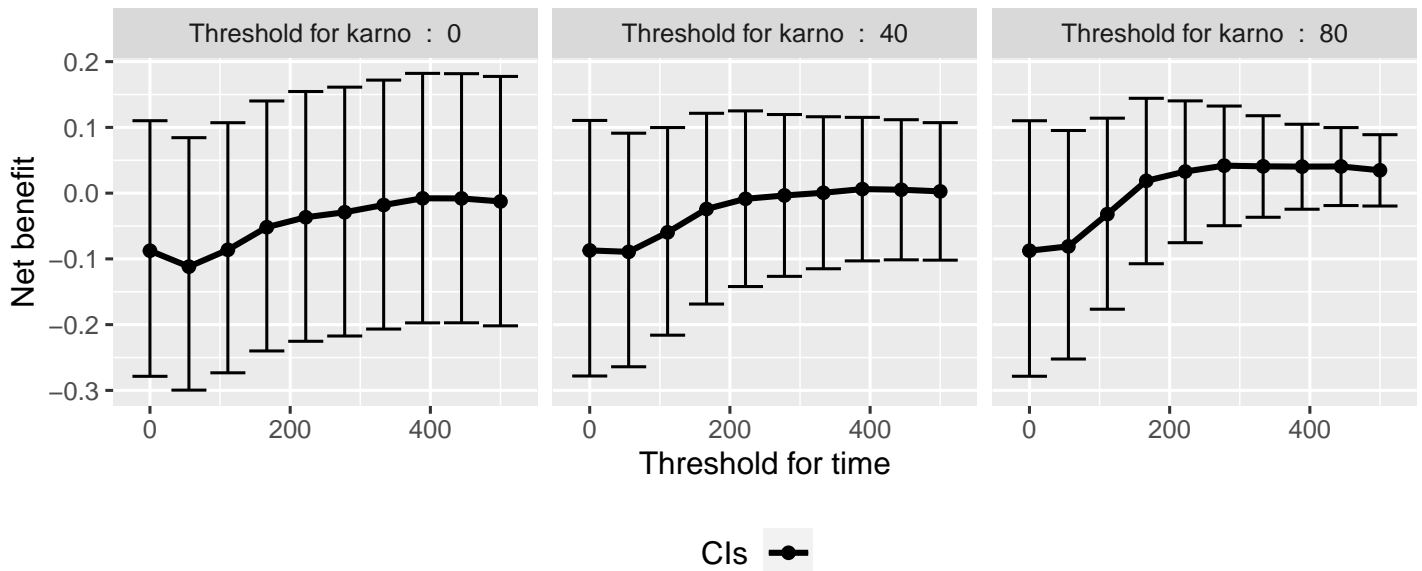
```

The latter should be used when the same endpoint is used at different priorities (each column correspond to the threshold that should be used at a priority). As before we can display the results using the autoplot function:

```

autoplot(BTse.H, col = NA)
## alternative display:
## autoplot(BTse.H, position = position_dodge(width = 15))

```



Note that the autoplot function cannot be used when more than 2 thresholds are varied at the same time.

2 Getting additional inside: looking at the pair level

So far we have looked at the overall score and probabilities. But it is also possible to extract the score relative to each pair, as well as to "manually" compute this score. This can give further inside on what the software is actually doing and what is the contribution of each individual on the evaluation of the treatment.

2.1 Extracting the contribution of each pair to the statistic

The net benefit or the win ratio statistics can be expressed as a sum of a score over all pairs of patients. The argument `keep.pairScore` enables to export the score relative to each pair in the output of `BuyseTest`:

```
form <- trt ~ tte(time, threshold = 20, status = "status") + cont(karno)
BT.keep <- BuyseTest(form,
  data = veteran, keep.pairScore = TRUE,
  trace = 0, method.inference = "none")
```

The method `getPairScore` can then be used to extract the contribution of each pair. For instance the following code extracts the contribution for the first endpoint:

```
getPairScore(BT.keep, endpoint = 1)
```

	index.1	index.2	favorable	unfavorable	neutral	uninf	weight
1:	1	70	1	0	0	0	1
2:	2	70	1	0	0	0	1
3:	3	70	1	0	0	0	1
4:	4	70	1	0	0	0	1
5:	5	70	1	0	0	0	1

4688:	65	137	0	1	0	0	1
4689:	66	137	0	1	0	0	1
4690:	67	137	0	1	0	0	1
4691:	68	137	0	1	0	0	1
4692:	69	137	0	1	0	0	1

Each line corresponds to different comparison between a pair from the control arm and the treatment arm. The column `strata` store to which strata the pair belongs (first, second, ...). The columns `favorable`, `unfavorable`, `neutral`, `uninformative` contains the result of the comparison, e.g. the first pair was classified as favorable while the last was classified as favorable with a weight of 1. The second and third columns indicates the rows in the original dataset corresponding to the pair:

```
veteran[c(70,1),]
```

	trt	celltype	time	status	karno	diagtime	age	prior
70	2	squamous	999	1	90	12	54	10
1	1	squamous	72	1	60	7	69	0

For the first pair, the event was observed for both observations and since $999 > 72 + 20$ the pair is rated favorable. Subtracting the average probability of the pair being favorable minus the average probability of the pair being unfavorable:

```
getPairScore(BT.keep, endpoint = 1)[, mean(favorable) - mean(unfavorable)]
```

```
[1] -0.08765836
```

gives the net benefit in favor of the treatment for the first endpoint:

```
BT.keep
```

```
endpoint threshold  delta  Delta
time           20 -0.0877 -0.0877
karno           -0.0133 -0.1009
```

More examples and explanation can be found in the documentation of the method `getPairScore`.

2.2 Extracting the survival probabilities

When using `scoring.rule` equals "Peron", survival probabilities at event time, and event times +/- threshold in the control and treatment arms are used to score the pair. Setting `keep.survival` to TRUE and `precompute` to FALSE in `BuyseTest.options` enables to export the survival probabilities in the output of `BuyseTest`:

```
BuyseTest.options(keep.survival = TRUE, precompute = FALSE)
BT.keep2 <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status") + cont(karno),
                      data = veteran, keep.pairScore = TRUE, scoring.rule = "Peron",
                      trace = 0, method.inference = "none")
```

The method `getSurvival` can then be used to extract these survival probabilities. For instance the following code extracts the survival for the first endpoint:

```
outSurv <- getSurvival(BT.keep2, endpoint = 1, strata = 1)
str(outSurv)
```

List of 5

```
$ survTimeC: num [1:69, 1:13] 72 411 228 126 118 10 82 110 314 100 ...
..- attr(*, "dimnames")=List of 2
.. ..$ : NULL
.. ..$ : chr [1:13] "time" "survivalC-threshold" "survivalC_0" "survivalC+threshold" ...
$ survTimeT: num [1:68, 1:13] 999 112 87 231 242 991 111 1 587 389 ...
..- attr(*, "dimnames")=List of 2
.. ..$ : NULL
.. ..$ : chr [1:13] "time" "survivalC-threshold" "survivalC_0" "survivalC+threshold" ...
$ survJumpC: num [1:57, 1:6] 3 4 7 8 10 11 12 13 16 18 ...
..- attr(*, "dimnames")=List of 2
.. ..$ : NULL
.. ..$ : chr [1:6] "time" "survival" "dSurvival" "index.survival" ...
$ survJumpT: num [1:51, 1:6] 1 2 7 8 13 15 18 19 20 21 ...
..- attr(*, "dimnames")=List of 2
.. ..$ : NULL
.. ..$ : chr [1:6] "time" "survival" "dSurvival" "index.survival" ...
$ lastSurv : num [1:2] 0 0
```

2.2.1 Computation of the score with only one censored event

Let's look at pair 91:

```
getPairScore(BT.keep2, endpoint = 1, rm.withinStrata = FALSE)[91]
```

```
index.1 index.2 indexWithinStrata.1 indexWithinStrata.2 favorable unfavorable neutral
1:      22      71                  22                  2          0  0.6950827 0.3049173
uninf weight
1:       0       1
```

In the dataset this corresponds to:

```
veteran[c(22,71),]
```

```
trt  celltype time status karno diagtime age prior
22   1 smallcell  97      0   60         5  67     0
71   2 squamous 112      1   80         6  60     0
```

The observation from the control group is censored at 97 while the observation from the treatment group has an event at 112. Since the threshold is 20, and $(112-20) < 97$, we know that the pair is not in favor of the treatment. The formula for probability in favor of the control is $\frac{S_c(97)}{S_c(112+20)}$. The survival at the event time in the censoring group is stored in `survTimeC`. Since observation 22 is the 22th observation in the control group:

```
iSurv <- outSurv$survTimeC[22,]
iSurv
```

```
time survivalC-threshold survivalC_0
97.0000000 0.5615232 0.5171924
survivalC+threshold survivalT-threshold survivalT_0
0.4235463 0.4558824 0.3643277
survivalT+threshold index.survivalC-threshold index.survivalC_0
0.2827500 25.0000000 28.0000000
index.survivalC+threshold index.survivalT-threshold index.survivalT_0
33.0000000 27.0000000 32.0000000
index.survivalT+threshold
35.0000000
```

Since we are interested in the survival in the control arm exactly at the event time:

```
Sc97 <- iSurv["survivalC_0"]
Sc97
```

```
survivalC_0
0.5171924
```

The survival at the event time in the treatment group is stored in `survTimeC`. Since observation 71 is the 2nd observation in the treatment group:

```
iSurv <- outSurv$survTimeT[2,] ## survival at time 112+20
iSurv
```

```

           time      survivalC-threshold      survivalC_0
112.0000000      0.5319693      0.4549201
survivalC+threshold      survivalT-threshold      survivalT_0
0.3594915      0.3801681      0.2827500
survivalT+threshold index.survivalC-threshold      index.survivalC_0
0.2827500      27.0000000      32.0000000
index.survivalC+threshold index.survivalT-threshold      index.survivalT_0
37.0000000      31.0000000      35.0000000
index.survivalT+threshold
35.0000000
```

Since we are interested in the survival in the control arm at the event time plus threshold:

```
Sc132 <- iSurv["survivalC+threshold"]
Sc132
```

```
survivalC+threshold
0.3594915
```

The probability in favor of the control is then:

```
Sc132/Sc97
```

```
survivalC+threshold
0.6950827
```

2.2.2 Computation of the score with two censored events

When both observations are censored, the formula for computing the probability in favor of treatment or control involves an integral. This integral can be computed using the function `calcIntegralSurv_cpp` that takes as argument a matrix containing the survival and the jumps in survival, e.g.:

```
head(outSurv$survJumpT)
```

```

      time  survival  dSurvival index.survival index.dsurrival1 index.dsurrival2
[1,]   1 0.7681159 -0.02941176         12         0         1
[2,]   2 0.7536232 -0.01470588         13         1         2
[3,]   7 0.7388463 -0.02941176         14         2         3
[4,]   8 0.7388463 -0.02941176         14         3         4
[5,]  13 0.7092924 -0.01470588         16         4         5
[6,]  15 0.6945155 -0.02941176         17         5         6
```

and the starting time of the integration time. For instance, let's look at pair 148:

```
getPairScore(BT.keep2, endpoint = 1, rm.withinStrata = FALSE)[148]
```

```

      index.1 index.2 indexWithinStrata.1 indexWithinStrata.2 favorable unfavorable neutral
1:         10      72                10                3 0.5058685   0.3770426 0.1170889
      uninfl weight
1:         0       1

```

which corresponds to the observations:

```
veteran[c(10,72),]
```

```

      trt celltype time status karno diagtime age prior
10    1 squamous  100      0   70         6  70     0
72    2 squamous   87      0   80         3  48     0

```

The probability in favor of the treatment (p_F) and control (p_{UF}) can be computed as:

$$p_F = -\frac{1}{S_T(x)S_C(y)} \int_{t>y} S_T(t+\tau) dS_C(t)$$

$$p_{UF} = -\frac{1}{S_T(x)S_C(y)} \int_{t>x} S_C(t+\tau) dS_T(t)$$

where $x = 87$ and $y = 100$. To ease the call of `calcIntegralScore_cpp` we create a warper:

```

calcInt <- function(...){ ## no need for the functionnal derivative of the score
  BuyseTest:::.calcIntegralSurv_cpp(...,
                                     returnDeriv = FALSE,
                                     derivSurv = matrix(0),
                                     derivSurvD = matrix(0))
}

```

and then call it to compute the probabilities:

```

denom <- as.double(outSurv$survTimeT[3,"survivalT_0"] * outSurv$survTimeC[10,"survivalC_0"])
M <- cbind("favorable" = -calcInt(outSurv$survJumpC, start = 100,
                                lastSurv = outSurv$lastSurv[2],
                                lastdSurv = outSurv$lastSurv[1])/denom,
          "unfavorable" = -calcInt(outSurv$survJumpT, start = 87,
                                   lastSurv = outSurv$lastSurv[1],
                                   lastdSurv = outSurv$lastSurv[2])/denom)
rownames(M) <- c("lowerBound","upperBound")
M

```

```

      favorable unfavorable
lowerBound 0.5058685   0.3770426
upperBound 0.5058685   0.3770426

```

Note: the lower bound is identical to the upper bound as we could estimate the full survival curve:

```
outSurv$lastSurv
```

```
[1] 0 0
```

3 Dealing with missing values or/and right censoring

In presence of censoring or missing values, it is often not possible to classify all pairs without a model for the censoring mechanism. The unclassified pairs, called uninformative, have a score of 0 which will typically bias the estimate of the net net benefit towards 0³. Consider the following dataset:

```
set.seed(10)
dt <- simBuyseTest(1e2, latent = TRUE, argsCont = NULL,
                  argsTTE = list(scale.T = 1/2, scale.C = 1,
                                scale.censoring.C = 1, scale.censoring.T = 1))
dt[, eventtimeCensoring := NULL]
dt[, status1 := 1]
head(dt)
```

	treatment	eventtimeUncensored	eventtime	status	toxicity	eta_toxicity	status1
1:	C	0.2135567	0.2135567	1	yes	-0.07945702	1
2:	C	0.3422379	0.3422379	1	no	1.18175155	1
3:	C	1.3933222	1.3933222	1	no	2.18614406	1
4:	C	0.6737702	0.1961599	0	no	0.40617493	1
5:	C	0.5642992	0.5642992	1	yes	-0.73835910	1
6:	C	1.1039218	0.1764950	0	yes	-1.95648670	1

where we have the uncensored event times (`eventtimeUncensored`) as well as the censored event times (`eventtime`). The percentage of censored observations is:

```
100*dt[,mean(status==0)]
```

```
[1] 44
```

We would like to be able to recover the net benefit estimated with the uncensored event times:

```
BuyseTest(treatment ~ tte(eventtimeUncensored, status1, threshold = 0.5),
          data = dt,
          scoring.rule = "Gehan", method.inference = "none", trace = 0)
```

	endpoint	threshold	Delta
eventtimeUncensored		0.5	-0.271

using the censored survival times.

³While the power is typically reduced, the type 1 error will still be controlled if censoring is at random

The `BuyseTest` function handles missing values via two arguments:

- `scoring.rule` indicates how pairs involving missing data are compared.
 - **the Gehan's scoring rule** compares the observed values. If it is not possible to decide whether one observation has a better endpoint than the other (e.g. because both are right-censoring) then the paired is scored uninformative.
 - **the Peron's scoring rule** compares the probability of one observation having a better endpoint than the other given the observed values. This requires a model for the censoring distribution. If the full survival curve can be identified then all pairs can be fully classified otherwise some of the pair will be partially uninformative.
- `correction.uninf` indicates what to do with the uninformative scores. Setting this argument to `TRUE` will re-distribute this score to favorable/unfavorable/neutral scores.

When the survival curve can be fully identified, the default (and recommended) approach is to use the Peron's scoring rule where the censoring model relies on Kaplan Meier curve is fitted in each treatment group. When the last observation are censored, then part of the survival curve is unknown and there is no perfect solution. One can:

- only use the Peron's scoring rule, which will lead to a non-0 uninformative score and therefore a "conservative" estimate of the net benefit.
- use the Peron's scoring rule in conjunction with the correction which will lead to an unbiased estimator if certain assumptions are met.
- only use the Peron's scoring rule with a parametric model which, if appropriate, will lead to an unbiased (and rather efficient) estimator.

3.1 Gehan's scoring rule

In the example, Gehan's scoring rule:

```
e.G <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
  data = dt, scoring.rule = "Gehan", trace = 0)
summary(e.G, print=FALSE)$table.print
```

	endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	Delta
1	eventtime	0.5	100	4.67	14.39	20.44	60.5	-0.0972
	CI [2.5% ; 97.5%]		p.value		significance			
1	[-0.1594;-0.0342]		0.0025149		**			

leads to many uninformative pairs (about 60%) and an estimate much closer to 0 than the truth.

3.2 Peron's scoring rule

In the example, Peron's scoring rule:

```
e.P <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
  data = dt, scoring.rule = "Peron", trace = 0)
summary(e.P, print=FALSE)$table.print
```

```
      endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%)   Delta
1 eventtime         0.5      100      11.17          43.34      44.12      1.37 -0.3216
  CI [2.5% ; 97.5%]    p.value significance
1  [-0.4584;-0.17] 5.3851e-05          ***
```

leads to no uninformative pairs. Indeed the last observation in each group is an (uncensored) event:

```
dt[,.SD[which.max(eventtime)],by="treatment"]
```

```
      treatment eventtimeUncensored eventtime status toxicity eta_toxicity status1
1:           C          2.668629  2.668629      1      yes  -1.9256436          1
2:           T          1.674053  1.588657      0      yes  -0.8647272          1
```

so the full survival curve could be identified. As a result the estimate is very close to the truth.

Note 1: the censoring model can be specified by first fitting a Kaplan Meier model for the survival time:

```
library(prodlim)
e.prodlim <- prodlim(Hist(eventtime, status) ~ treatment, data = dt)
```

Then passing the model to the `BuyseTest` via the `model.tte` argument:

```
e.P1 <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
  model.tte = e.prodlim,
  data = dt, scoring.rule = "Peron", trace = 0)
summary(e.P1, print=FALSE)$table.print
```

```
      endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%)   Delta
1 eventtime         0.5      100      11.17          43.34      44.12      1.37 -0.3216
  CI [2.5% ; 97.5%]    p.value significance
1  [-0.4187;-0.2173] 6.5701e-09          ***
```

Note that the CI/p-value have changed since, unless stated otherwise, `BuyseTest` assumes no uncertainty about the survival model when using `model.tte`. One can force it to account for the uncertainty adding an attribute:

```
attr(e.prodlim, "iidNuisance") <- TRUE
e.P2 <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
  model.tte = e.prodlim,
  data = dt, scoring.rule = "Peron", trace = 0)
summary(e.P2, print=FALSE)$table.print
```

	endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	Delta
1	eventtime	0.5	100	11.17	43.34	44.12	1.37	-0.3216
	CI [2.5% ; 97.5%]		p.value	significance				
1		[-0.4584;-0.17]	5.3851e-05					***

Note 2: it is possible to use a parametric model via the `survreg` function:

```
library(survival)
e.survreg <- survreg(Surv(eventtime, status) ~ treatment, data = dt,
                     dist = "weibull")
attr(e.survreg, "iidNuisance") <- TRUE
```

Then passing the model to the `BuyseTest` via the `model.tte` argument:

```
e.P3 <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                  model.tte = e.survreg,
                  data = dt, scoring.rule = "Peron", trace = 0)
summary(e.P3, print=FALSE)$table.print
```

	endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	Delta
1	eventtime	0.5	100	11.88	34.19	53.92	0.01	-0.2231
	CI [2.5% ; 97.5%]		p.value	significance				
1		[-0.3455;-0.0932]	0.00085702					***

Internally the survival curve is discretized using 1000 points starting from survival = 1 to survival = 0.001 (this is why there is a non-0 but small percentage of uninformative pairs). This is performed internally by applying the `BuyseTTEM` method. Another discretisation can be obtained by calling `BuyseTTEM` with another value for the `n.grid` argument:

```
e.TTEM <- BuyseTTEM(e.survreg, treatment = "treatment", iid = TRUE, n.grid = 2500)
attr(e.TTEM, "iidNuisance") <- TRUE
str(e.TTEM$peron$jumpSurvHaz[[1]][[1]])
```

```
'data.frame':      2500 obs. of  3 variables:
 $ index.jump: logi  NA NA NA NA NA NA ...
 $ time.jump : num   0 0.000307 0.000632 0.000964 0.001301 ...
 $ survival  : num   1 1 0.999 0.999 0.998 ...
```

and then passing to `BuyseTest`:

```
e.P4 <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                  model.tte = e.TTEM,
                  data = dt, scoring.rule = "Peron", trace = 0)
summary(e.P4, print=FALSE)$table.print
```

	endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	Delta
1	eventtime	0.5	100	11.87	34.18	53.94	0.01	-0.2231
	CI [2.5% ; 97.5%]		p.value	significance				
1		[-0.3455;-0.0932]	0.00085776					***

It is therefore possible to extend the approach to other model by defining an appropriate `BuyseTTEM` method. Looking at the code use for defining `BuyseTTEM.survreg` can be helpful.

3.3 Correction via inverse probability-of-censoring weights (IPCW)

With IPCW, the weights of the non-informative pairs is redistributed to the informative pairs. This is only a good strategy when there are no neutral pairs or there are no lower priority endpoints. This gives an estimate much closer to the true net benefit:

```
BT <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
               data = dt, keep.pairScore = TRUE, trace = 0,
               scoring.rule = "Gehan", method.inference = "none", correction.uninf = 2)
summary(BT)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- treatment groups: T (treatment) vs. C (control)
- censored pairs  : deterministic score or uninformative
- uninformative pairs: no contribution, their weight is passed to the informative pairs using IPCW
- results
  endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) Delta
eventtime      0.5      100      11.82      36.43      51.75      0 -0.2461
```

We can also see that no pair is finally classified as non informative. To get some inside about the correction we can look at the scores of the pairs:

```
iScore <- getPairScore(BT, endpoint = 1)
```

To get a synthetic view, we only look at the unique favorable/unfavorable/neutral/uninformative results:

```
iScore[,.SD[1],
        .SDcols = c("favorableC","unfavorableC","neutralC","uninfC"),
        by = c("favorable","unfavorable","neutral","uninf")]
```

	favorable	unfavorable	neutral	uninf	favorableC	unfavorableC	neutralC	uninfC
1:	0	0	1	0	0.000000	0.000000	2.531646	0
2:	0	1	0	0	0.000000	2.531646	0.000000	0
3:	0	0	0	1	0.000000	0.000000	0.000000	0
4:	1	0	0	0	2.531646	0.000000	0.000000	0

We can see that the favorable/unfavorable/neutral pairs have seen their contribution multiplied by:

```
iScore[,1/mean(favorable + unfavorable + neutral)]
```

```
[1] 2.531646
```

i.e. the inverse probability of being informative.

3.4 Correction at the pair level

Another possible correction is to distribute the non-informative weight of a pair to the average favorable/unfavorable/neutral probability observed on the sample:

```
BT <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
               data = dt, keep.pairScore = TRUE, trace = 0,
               scoring.rule = "Gehan", method.inference = "none", correction.uninf = TRUE)
summary(BT)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)
- null hypothesis : Delta == 0
- treatment groups: T (treatment) vs. C (control)
- censored pairs  : deterministic score or uninformative
- uninformative pairs: score equals the averaged score of all informative pairs
- results
  endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%)  Delta
eventtime      0.5      100      11.82      36.43      51.75      0 -0.2461
```

Looking at the scores of the pairs:

```
iScore <- getPairScore(BT, endpoint = 1)
iScore[,.SD[1],
       .SDcols = c("favorableC","unfavorableC","neutralC","uninfC"),
       by = c("favorable","unfavorable","neutral","uninf")]
```

	favorable	unfavorable	neutral	uninf	favorableC	unfavorableC	neutralC	uninfC
1:	0	0	1	0	0.0000000	0.0000000	1.0000000	0
2:	0	1	0	0	0.0000000	1.0000000	0.0000000	0
3:	0	0	0	1	0.1182278	0.3643038	0.5174684	0
4:	1	0	0	0	1.0000000	0.0000000	0.0000000	0

we can see that the corrected probability have not changed for the informative pairs, but for the non-informative they have been set to:

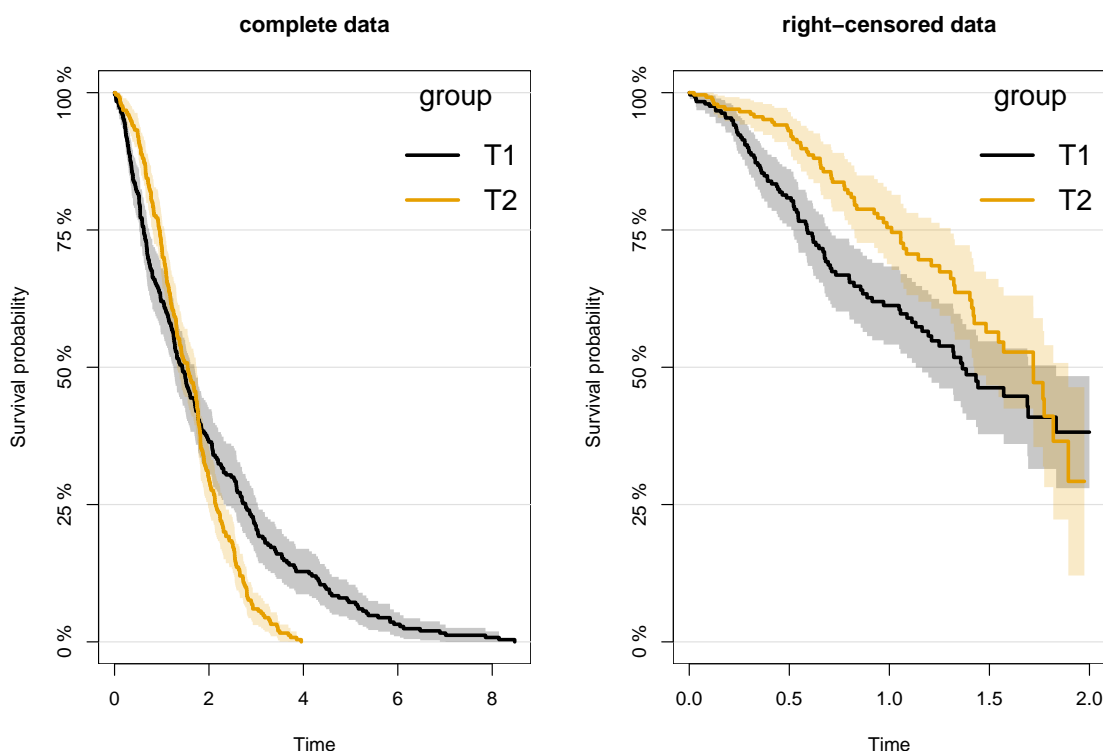
```
iScore[, .(favorable = weighted.mean(favorable, w = 1-uninf),
      unfavorable = weighted.mean(unfavorable, w = 1-uninf),
      neutral = weighted.mean(neutral, w = 1-uninf))]
```

	favorable	unfavorable	neutral
1:	0.1182278	0.3643038	0.5174684

3.5 Note on the use of the corrections

As mentioned in [Péron et al. \(2021\)](#), the corrections (at the pair level or IPCW) are assumes that uninformative pairs would on average behave like informative pairs. This is typically the case under the proportional hazard assumption. However that may not be the case with other distributions, e.g.:

```
set.seed(10); n <- 250;
df <- rbind(data.frame(group = "T1", time = rweibull(n, shape = 1, scale = 2), status = 1),
            data.frame(group = "T2", time = rweibull(n, shape = 2, scale = 1.8), status = 1))
df$censoring <- runif(NROW(df), 0, 2)
df$timeC <- pmin(df$time, df$censoring)
df$statusC <- as.numeric(df$time <= df$censoring)
plot(prodlim(Hist(time, status) ~ group, data = df)); title("complete data");
plot(prodlim(Hist(timeC, statusC) ~ group, data = df)); title("right-censored data");
```



Here the net benefit that we would have estimated with complete data:

```
BuyseTest.options(method.inference = "none")
e.ref <- BuyseTest(group ~ tte(time,status), data = df, trace = FALSE)
s.ref <- summary(e.ref, print = FALSE)$table[1,c("favorable", "unfavorable", "neutral", "uninf", "
Delta")]
s.ref
```

	favorable	unfavorable	neutral	uninf	Delta
1	50.2048	49.7952	0	0	0.004096

can be taken as a reference. Violation of the assumption will in this example have a substantial impact and lead to a worse estimate with the correction:

```
e.correction <- BuyseTest(group ~ tte(timeC,statusC)+cont(time), data = df, trace = FALSE,
  correction.uninf = TRUE)
s.correction <- summary(e.correction, print = FALSE)$table[1,c("favorable","unfavorable","
  neutral","uninf","Delta")]
```

Warning message:

```
In .BuyseTest(envir = envirBT, iid = outArgs$iid, method.inference = "none",  :
```

Some of the survival curves for endpoint(s) "timeC" are unknown beyond a survival of 0.25.
The correction of uninformative pairs assume that uninformative pairs would on average behave like
This can be a strong assumption and have substantial impact when the tail of the survival curve is

than without:

```
e.Peron <- BuyseTest(group ~ tte(timeC,statusC), data = df, trace = FALSE)
s.Peron <- summary(e.Peron,print = FALSE)$table[1,c("favorable","unfavorable","neutral","uninf
  ","Delta")]
rbind("reference" = s.ref,
  "no correction" = s.Peron,
  "correction" = s.correction)
```

	favorable	unfavorable	neutral	uninf	Delta
reference	50.20480	49.79520	0	0.00000	0.00409600
no correction	49.09253	39.74775	0	11.15972	0.09344778
correction	55.25931	44.74069	0	0.00000	0.10518628

4 Simulating data using `simBuyseTest`

You can simulate data with the `simBuyseTest` function. For instance the following code simulates data for 5 individuals in the treatment arm and 5 individuals in the control arm:

```
set.seed(10)
simBuyseTest(n.T = 5, n.C = 5)
```

	treatment	eventtime	status	toxicity	score
1:	C	0.60539304	0	yes	-1.85374045
2:	C	0.31328027	1	yes	-0.07794607
3:	C	0.03946623	0	yes	0.96856634
4:	C	0.32147489	1	yes	0.18492596
5:	C	1.57044952	0	yes	-1.37994358
6:	T	0.29069131	0	no	1.10177950
7:	T	0.19522131	0	yes	0.75578151
8:	T	0.04640668	0	yes	-0.23823356
9:	T	0.05277335	1	yes	0.98744470
10:	T	0.43062009	1	yes	0.74139013

By default a categorical, continuous and time to event outcome are generated independently. You can modify their distribution via the arguments `argsBin`, `argsCont`, `argsTTE`. For instance the following code simulates two continuous variables with mean 5 in the treatment arm and 10 in the control arm all with variance 1:

```
set.seed(10)
argsCont <- list(mu.T = c(5,5), mu.C = c(10,10),
                 sigma.T = c(1,1), sigma.C = c(1,1),
                 name = c("tumorSize", "score"))
dt <- simBuyseTest(n.T = 5, n.C = 5,
                  argsCont = argsCont)
dt
```

	treatment	eventtime	status	toxicity	tumorSize	score
1:	C	0.1805891	0	yes	11.086551	8.564486
2:	C	0.1702538	1	yes	9.237455	10.362087
3:	C	0.2621793	1	no	9.171337	8.240913
4:	C	0.2959301	0	no	10.834474	9.675456
5:	C	0.4816549	1	yes	9.032348	9.348437
6:	T	0.6446131	1	no	5.089347	6.101780
7:	T	0.7372264	1	yes	4.045056	5.755782
8:	T	0.7213402	0	yes	4.804850	4.761766
9:	T	0.1580651	1	yes	5.925521	5.987445
10:	T	0.2212117	0	yes	5.482979	5.741390

This functionality is based on the `sim` function of the `lava` package (<https://github.com/kkholst/lava>)

5 Power calculation using powerBuyseTest

The function `powerBuyseTest` can be used to perform power calculation, i.e., estimate the probability of rejecting a null hypothesis under a specific generative mechanism. The user therefore need to specify:

- the generative mechanism via a function - argument `sim`
- the null hypothesis - argument `null`
- the sample size(s) for the which the power should be computed - argument `sample.size`

Consider the following generative mechanism where the outcome follows a Student's t-distribution in the treatment and control group, with same variance and degrees of freedom but different mean:

```
simFCT <- function(n.C, n.T){  
  out <- rbind(cbind(Y=stats::rt(n.C, df = 5), group=0),  
              cbind(Y=stats::rt(n.T, df = 5) + 1/2, group=1))  
  return(data.table::as.data.table(out))  
}  
simFCT(101,101)
```

```
      Y group  
1: -0.5080164    0  
2:  1.3917774    0  
3:  1.2909425    0  
4:  1.1812472    0  
5:  0.6935526    0  
---  
198: -0.0193772    1  
199: -1.0573662    1  
200: -0.7772939    1  
201:  0.1583587    1  
202:  4.7379910    1
```

We then define the null hypothesis:

```
null <- c("netBenefit" = 0)
```

Naming the value is important since that will indicate which statistic should be used (here the net benefit). We can assess the power of a test based on the net benefit using the following syntax:

```
powerW <- powerBuyseTest(sim = simFCT, method.inference = "u-statistic", null = null,  
                        sample.size = c(5,10,20,30,50,100),  
                        formula = group ~ cont(Y),  
                        n.rep = 1000, seed = 10, cpus = 6, trace = 0)
```

And use the summary method to display the power (column `rejection.rate`):

```
summary(powerW)
```

Simulation study with Generalized pairwise comparison
with 1000 samples

```
- statistic : net benefit (null hypothesis Delta=0)
endpoint threshold n.T n.C mean.estimate sd.estimate mean.se rejection.rate
      Y      1e-12   5   5          0.2337          0.3831  0.3342          0.078
              10  10          0.2488          0.2747  0.2439          0.158
              20  20          0.2475          0.1832  0.1753          0.253
              30  30          0.2474          0.1503  0.1434          0.377
              50  50          0.2411          0.1161  0.1114          0.542
              100 100         0.2433          0.0829  0.0787          0.837

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)
```

It is also possible to use an asymptotic approximation to derive a approximate sample size satisfying a specific type 1 and type 2 error rate:

```
nW <- powerBuyseTest(sim = simFCT, method.inference = "u-statistic", null = null,
                     power = 0.8, max.sample.size = 10000,
                     formula = group ~ cont(Y),
                     n.rep = 1000, seed = 10, cpus = 6, trace = 0)
summary(nW)
```

Simulation study with Generalized pairwise comparison
with 1000 samples

```
- statistic : net benefit (null hypothesis Delta=0)
endpoint threshold n.T n.C mean.estimate sd.estimate mean.se rejection.rate
      Y      1e-12  91  91          0.2394          0.0847  0.0826          0.799

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)
```

This procedure is inspired from the procedure presented by [Brunner et al. \(2018\)](#) in section 3.8.2.2.

6 Modifying default options

The `BuyseTest.options` method enable to get and set the default options of the `BuyseTest` function. For instance, the default option for trace is:

```
BuyseTest.options("trace")
```

```
$trace  
[1] 2
```

To change the default option to 0 (i.e. no output) use:

```
BuyseTest.options(trace = 0)
```

To change what the results output by the summary function use:

```
BuyseTest.options(summary.display = list(c("endpoint", "threshold", "delta", "Delta", "information  
(%)")))  
summary(BT)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net benefit (delta: endpoint specific, Delta: global)  
- null hypothesis : Delta == 0  
- treatment groups: T (treatment) vs. C (control)  
- censored pairs  : deterministic score or uninformative  
- uninformative pairs: score equals the averaged score of all informative pairs  
- results  
  endpoint threshold  Delta information(%)  
eventtime      0.5 -0.2461      100
```

To restore the original default options do:

```
BuyseTest.options(reinitialise = TRUE)
```

References

- Brunner, E., Bathke, A. C., and Konietzschke, F. (2018). *Rank and pseudo-rank procedures for independent observations in factorial designs*. Springer.
- Buyse, M. (2010). Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. *Statistics in medicine*, 29(30):3245–3257.
- Dong, G., Qiu, J., Wang, D., and Vandemeulebroecke, M. (2018). The stratified win ratio. *Journal of biopharmaceutical statistics*, 28(4):778–796.
- Ozenne, B., Budtz-Jørgensen, E., and Péron, J. (2021). The asymptotic distribution of the net benefit estimator in presence of right-censoring. *Statistical methods in medical research*, 30(11):2399–2412.
- Péron, J., Buyse, M., Ozenne, B., Roche, L., and Roy, P. (2018). An extension of generalized pairwise comparisons for prioritized outcomes in the presence of censoring. *Statistical methods in medical research*, 27(4):1230–1239.
- Péron, J., Idlhaj, M., Maucourt-Boulch, D., Giaï, J., Roy, P., Collette, L., Buyse, M., and Ozenne, B. (2021). Correcting the bias of the net benefit estimator due to right-censored observations. *Biometrical Journal*, 63(4):893–906.
- Verbeeck, J., Spitzer, E., de Vries, T., van Es, G., Anderson, W., Van Mieghem, N., Leon, M., Molenberghs, G., and Tijssen, J. (2019). Generalized pairwise comparison methods to analyze (non) prioritized composite endpoints. *Statistics in medicine*.