

Overview of the package **BuyseTest**

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This vignette describes the main functionalities of the **BuyseTest** package, focusing on software (and not statistical) aspects, and assume that the reader is familiar with the GPC framework ¹.

The **BuyseTest** 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 and [Piffoux et al. \(2024\)](#) to incorporate a restriction time. 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 $\mathbb{P}[X \geq Y + \tau]$. Their difference $\mathbb{P}[Y \geq X + \tau] - \mathbb{P}[X \geq Y + \tau]$ leads to the net treatment benefit² and their ratio $\frac{\mathbb{P}[Y \geq X + \tau]}{\mathbb{P}[X \geq Y + \tau]}$ to the win ratio. The software also evaluate the proportion of neutral pairs $\mathbb{P}[|X - Y| < \tau]$ and which can be included to obtain the probabilistic index $\mathbb{P}[Y \geq X + \tau] + 0.5\mathbb{P}[|X - Y| < \tau]$ or win odds $\frac{\mathbb{P}[Y \geq X + \tau] + 0.5\mathbb{P}[|X - Y| < \tau]}{\mathbb{P}[X \geq Y + \tau] + 0.5\mathbb{P}[|X - Y| < \tau]}$.

- 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 treatment 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).
 - **nobs** to extract the number of observations and pairs.
 - **getIid** to extract the iid decomposition of the estimator.
 - **getPairScore** to extract the contribution of each pair in a data.frame format (long format).
 - **getMatrixScore** to extract the contribution of each pair in a matrix format (squared format).
 - **getSurvival** to extract the estimates of the survival used for right-censored endpoints.
 - **BuyseMultComp** to adjust p-values and confidence intervals for multiple comparisons.

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

²in absence of ties and for an infinitesimal τ the testing whether the net treatment benefit is 0 is equivalent the Wilcoxon-Mann-Whitney parameter

- 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.

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

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

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

```
data(cancer, package = "survival")
veteran <- cbind(id = 1:NROW(veteran), veteran)
veteran$trt <- factor(veteran$trt, 1:2, c("Pl", "Exp"))
head(veteran)
```

	id	trt	celltype	time	status	karno	diagtime	age	prior
1	1	Pl	squamous	72	1	60	7	69	0
2	2	Pl	squamous	411	1	70	5	64	10
3	3	Pl	squamous	228	1	60	3	38	0
4	4	Pl	squamous	126	1	60	9	63	10
5	5	Pl	squamous	118	1	70	11	65	10
6	6	Pl	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] '3.3.9'
```

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

```
sessionInfo()
```

```
R version 4.5.3 (2026-03-11)
```

```
Platform: x86_64-pc-linux-gnu
```

```
Running under: Ubuntu 22.04.5 LTS
```

```
Matrix products: default
```

```
BLAS: /usr/lib/x86_64-linux-gnu/blas/libblas.so.3.10.0
```

```
LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.10.0 LAPACK version 3.10.0
```

```
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

```

```

time zone: Europe/Copenhagen
tzcode source: system (glibc)

```

attached base packages:

```

[1] stats      graphics  grDevices  utils      datasets  methods    base

```

other attached packages:

```

[1] prodlim_2026.03.11  ggplot2_4.0.2      survival_3.5-8      BuyseTest_3.3.9
[5] butils.base_1.3     Rcpp_1.1.1-1       devtools_2.5.1      usethis_3.2.1
[9] data.table_1.18.2.1

```

loaded via a namespace (and not attached):

```

[1] tidyselect_1.2.1      dplyr_1.2.1         farver_2.1.2
[4] S7_0.2.1-1           fastmap_1.2.0       TH.data_1.1-5
[7] digest_0.6.39        rpart_4.1.23        lifecycle_1.0.5
[10] cluster_2.1.6         ellipsis_0.3.3      magrittr_2.0.5
[13] compiler_4.5.3        rlang_1.2.0         Hmisc_5.2-5
[16] doSNOW_1.0.20         tools_4.5.3         knitr_1.51
[19] htmlwidgets_1.6.4     timereg_2.0.7       pkgbuild_1.4.8
[22] xml2_1.5.2            RColorBrewer_1.1-3  multcomp_1.4-30
[25] pkgload_1.5.1         polyspline_1.1.25    withr_3.0.2
[28] foreign_0.8-86        purrr_1.2.2         numDeriv_2016.8-1.1
[31] desc_1.4.3            nnet_7.3-19         grid_4.5.3
[34] stats4_4.5.3          roxygen2_7.3.3      mets_1.3.9
[37] colorspace_2.1-2      future_1.70.0        riskRegression_2026.05.19
[40] MASS_7.3-60.0.1       globals_0.19.1      scales_1.4.0
[43] iterators_1.0.14      cli_3.6.6           mvtnorm_1.3-7
[46] rmarkdown_2.31        rms_8.1-1           generics_0.1.4
[49] otel_0.2.0            rstudioapi_0.18.0   future.apply_1.20.2
[52] RcppArmadillo_15.2.4-1 sessioninfo_1.2.3    cachem_1.1.0
[55] stringr_1.6.0         splines_4.5.3        parallel_4.5.3
[58] base64enc_0.1-6       vctrs_0.7.3         sandwich_3.1-1
[61] glmnet_4.1-10         Matrix_1.6-5         SparseM_1.84-2
[64] Formula_1.2-5         htmlTable_2.4.3      listenv_0.10.1
[67] foreach_1.5.2         cmprsk_2.2-12        snow_0.4-4
[70] glue_1.8.1            parallelly_1.47.0    codetools_0.2-19
[73] stringi_1.8.7         shape_1.4.6.1        gtable_0.3.6
[76] tibble_3.3.1          pillar_1.11.1        quantreg_6.1
[79] htmltools_0.5.9       lava_1.9.0           R6_2.6.1
[82] rprojroot_2.1.1       evaluate_1.0.5       lattice_0.22-5
[85] backports_1.5.1       memoise_2.0.1        MatrixModels_0.5-4
[88] nlme_3.1-163          gridExtra_2.3        checkmate_2.3.4
[91] xfun_0.57             zoo_1.8-15           fs_2.1.0
[94] pkgconfig_2.0.3

```

1 Performing generalized pairwise comparisons (GPC)

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. 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 = Pl and Treatment = Exp
- 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
(non-parametric, group-specific)

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, endpoints are wrapped by parentheses, preceded by a character string indicated their type:
 - binary (**b**, **bin**, or **binary**)
 - continuous (**c**, **cont**, or **continuous**)
 - time to event (**t**, **tte**, or **timetoevent**)

For instance:

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

where we also set the argument `trace` to `FALSE` to execute silently the function. 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 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: Exp (treatment) vs. Pl (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
```

It displays information about each endpoint, percentage of pairs classified as favorable, unfavorable, neutral, and uninformative, as well as the estimated net treatment benefit (column `Delta`), its confidence interval, and the corresponding p-value testing the absence of a group difference. To display the number of pairs instead of the percentage of pairs that are favorable/unfavorable/neutral/uninformative, one can set the argument `percentage` to `FALSE`. See `help(S4BuyseTest-summary)` for more details about the `summary` method, its input and output.

The `print` method provides a more concise display of the results:

```
print(BT, percentage = FALSE)
```

```
endpoint threshold total favorable unfavorable neutral uninf   Delta CI [2.5% ; 97.5%]  
time          +20 4692  1772.59    2183.89 735.52      0 -0.0877  [-0.2735;0.1045]  
p.value  
0.37162
```

The `model.tables` method outputs the information from the previous table 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
```

1.2 What about other summary statistics?

Results for other summary statistics are also accessible:

- argument `statistic`

- proportion in favor of treatment (`favorable`): $\mathbb{P}[Y \geq X + \tau]$
- proportion in favor of control (`unfavorable`): $\mathbb{P}[X \geq Y + \tau]$
- win ratio (`winRatio`): $\frac{\mathbb{P}[Y \geq X + \tau]}{\mathbb{P}[X \geq Y + \tau]}$

For instance, to display the estimated win ratio instead of the estimated net treatment benefit, use:

```
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: Exp (treatment) vs. Pl (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
```

⚠ In presence of ties, the null distribution of the proportion in favor of treatment or control depends on the data generative mechanism and the threshold of clinical relevance. This is why, unless the argument `null` is provided by the user, the `confint` method will not produce any `p.value`:

```
confint(BT, statistic = "favorable")
```

```
      estimate      se lower.ci upper.ci null p.value
time_t20 0.3777905 0.04902199 0.2874747 0.477467  NA      NA
```

A permutation test may be used to empirically estimate a value for the null hypothesis:

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

```
      estimate      se lower.ci upper.ci      null      p.value
time_t20 0.3777905 0.04770182      NA      NA 0.4205855 0.3636364
```

which, in this example, is around 0.42.

⚠ Testing an inadequate null hypothesis can have dramatic consequences on the p-value:

```
rbind(confint(BT, statistic = "favorable", null = 0.42),
      confint(BT, statistic = "favorable", null = 0.5))
```

```
      estimate      se lower.ci upper.ci null      p.value
time_t20 0.3777905 0.04902199 0.2874747 0.477467 0.42 0.39826735
time_t201 0.3777905 0.04902199 0.2874747 0.477467 0.50 0.01673643
```

Considering the proportion of neutral pairs in the summary statistics: - argument `add.halfNeutral`

- Wilcoxon-Mann-Whitney parameter or probabilistic index: $\mathbb{P}[Y \geq X + \tau] + 0.5 \mathbb{P}[|Y - X| < \tau]$.
- win odds: $\frac{\mathbb{P}[Y \geq X + \tau] + 0.5 \mathbb{P}[|Y - X| < \tau]}{\mathbb{P}[X \geq Y + \tau] + 0.5 \mathbb{P}[|Y - X| < \tau]}$.

have been recommended (e.g. [Ajufu et al. \(2023\)](#)) over the win ratio. These summary statistics can be output by specifying the argument `add.halfNeutral` to `TRUE` when calling `BuyseTest`:

```
BT.half <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
                    data = veteran, trace = FALSE, add.halfNeutral = TRUE)
confint(BT.half, statistic = "favorable")
```

```
      estimate      se lower.ci upper.ci null  p.value
time_t20 0.4561708 0.04880921 0.3632263 0.5522714 0.5 0.3716632
```

```
confint(BT.half, statistic = "winRatio")
```

```
      estimate      se lower.ci upper.ci null  p.value
time_t20 0.8388127 0.1650208 0.5704361 1.233454 1 0.3716211
```

Testing a net treatment benefit of 0, a win odds of 1, or a Wilcoxon-Mann-Whitney parameter of 0.5 corresponds to the same hypothesis and therefore the same p-value should be obtained. The (small) discrepancy in p-values observed in this example (0.371617 vs. 0.3716211 vs. 0.3716632) are due to small sample approximations. Such discrepancies will not arise when using non-parametric bootstrap or permutation tests using quantiles of the bootstrap or permutation distribution, e.g.:

```
BT.halfboot <- BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
                        data = veteran, trace = FALSE, add.halfNeutral = TRUE,
                        method.inference = "bootstrap", seed = 10)
Mstat <- rbind(netBenefit = confint(BT.halfboot, statistic = "netBenefit"),
              winRatio = confint(BT.halfboot, statistic = "winRatio"),
              favorable = confint(BT.halfboot, statistic = "favorable"))
Mstat
```

```
      estimate      se lower.ci upper.ci null p.value
netBenefit -0.08765836 0.10021632 -0.2720510 0.1033974 0.0 0.383
winRatio    0.83881270 0.17440155 0.5722640 1.2306429 1.0 0.383
favorable   0.45617082 0.05010816 0.3639745 0.5516987 0.5 0.383
```


1.3 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 this variable wrapped by parenthesis and preceded by the character string **strata** in the formula:

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

When doing a stratified analysis, the summary method displays strata-specific and global results³:

```
keep.colStrata <- c("endpoint", "strata", "total",
                   "favorable", "unfavorable", "neutral", "uninf", "delta", "Delta")
summary(BTstrata, type.display = keep.colStrata)
```

Generalized pairwise comparisons with 1 endpoint and 4 strata

```
- 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: Exp (treatment) vs. Pl (control)
- strata weights : 26.38%, 34.63%, 18.47%, 20.52%
- uninformative pairs: no contribution
- results
```

endpoint	strata	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	delta	Delta
time	global	100.00	36.06	45.77	17.33	0.85	-0.0997	-0.0997
	squamous	25.38	14.33	8.77	2.28	0.00	0.2193	
	smallcell	45.69	12.69	20.88	11.27	0.85	-0.1792	
	adeno	13.71	4.74	6.15	2.81	0.00	-0.1034	
	large	15.23	4.30	9.97	0.96	0.00	-0.3722	

The percentage of pairs in the total/favorable/unfavorable/neutral/uninf columns are relative to the overall number of pairs whereas the column **delta** presents the endpoint and strata-specific net treatment benefits (in the last 4 lines). The last column (**Delta**) displays the global (i.e. pooled over strata), conditional, net treatment benefit.

⚠ With the default way of pooling results across strata, the proportion of favorable pairs minus the proportion of unfavorable pairs (36.06%-45.77%=9.71%) does not equal the global net treatment benefit (9.97%). To retrieve this value of the Net Treatment Benefit, one should first extract the number of pairs per strata using the method **nobs**:

```
strata.obs <- as.data.frame(nobs(BTstrata, strata = TRUE))
strata.obs
```

```
      Pl Exp pairs
squamous 15 20 300
```

³the strata-specific results can be removed by setting the argument **strata** to "global" when calling **summary**.

```
smallcell 30 18 540
adeno      9 18 162
large      15 12 180
```

and use the method `model.tables` to extract the number of favorable and unfavorable pairs per strata:

```
dfStrata <- model.tables(BTstrata, percentage = FALSE,
                        strata = c("squamous", "smallcell", "adeno", "large"),
                        columns = c("strata", "total", "favorable", "unfavorable"))
dfStrata
```

```
      strata total favorable unfavorable
1  squamous   300 169.40260    103.6104
2 smallcell   540 150.00000    246.7778
3     adeno   162  56.00000     72.7500
4     large   180  50.83333    117.8333
```

We retrieve the strata-specific net treatment benefits by comparing, in each strata, the number of favorable and unfavorable pairs relative to the number of pairs⁴:

```
delta <- (dfStrata$favorable - dfStrata$unfavorable)/strata.obs$pairs
delta
```

```
[1] 0.2193074 -0.1792181 -0.1033951 -0.3722222
```

The global net treatment benefit is then the sum of the strata-specific net treatment benefits weighted by the strata weights:

```
weightCMH <- strata.obs$pairs/(strata.obs$P1 + strata.obs$Exp)


list(estimate = sum(delta * weightCMH/sum(weightCMH)),
     weight = 100*weightCMH/sum(weightCMH))
```

```
$estimate
```

```
[1] -0.09967584
```

```
$weight
```

```
[1] 26.38329 34.62807 18.46830 20.52034
```

 The approach is also applicatble to the probabilistic index but not to the win ratio/odds: the ratio between the global proportions is taken, i.e., pooling is performed at the numerator and at the denominator instead of pooling fractions - see [Dong et al. \(2018\)](#), equation 1.

⁴Alernatively one could compute, from the `summary`, the difference between the percentage of favorable and unfavorable pairs relative to the percentage of pairs in the strata, e.g. $(14.33\% - 8.77\%)/25.38\% \approx 21.93\%$

The default weighting scheme is CMH, standing for Cochran-Mantel-Haenszel, which has been recommended in the literature (Dong et al., 2018). It is efficient under the assumption of a common multiplicative effect (across strata) on the odds ratio scale.

Other weighting schemes can be used.

- argument `pool.strata`.

When considering additive effect, one should instead weight proportionally to the number of pairs:

```
BTstrata2 <- BuyseTest(ffstrata, data = veteran, trace = 0, pool.strata = "buyse")
summary(BTstrata2, type.display = keep.colStrata)
```

Generalized pairwise comparisons with 1 endpoint and 4 strata

```
- 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: Exp (treatment) vs. Pl (control)
- strata weights : 25.38%, 45.69%, 13.71%, 15.23%
- uninformative pairs: no contribution
- results
```

endpoint	strata	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	delta	Delta
time	global	100.00	36.06	45.77	17.33	0.85	-0.0971	-0.0971
	squamous	25.38	14.33	8.77	2.28	0.00	0.2193	
	smallcell	45.69	12.69	20.88	11.27	0.85	-0.1792	
	adeno	13.71	4.74	6.15	2.81	0.00	-0.1034	
	large	15.23	4.30	9.97	0.96	0.00	-0.3722	

The strata-specific net treatment benefits are unchanged: the weighting scheme only affects the evaluation of the overall net treatment benefit. With this weighting scheme it now equals the difference between the overall proportion of favorable vs. unfavorable pairs (36.06%-45.77%). While extractors will by default output global estimates (i.e. after pooling the results over strata)

```
confint(BTstrata2)
```

	estimate	se	lower.ci	upper.ci	null	p.value
time_t20	-0.09706901	0.0977929	-0.2829348	0.09582321	0	0.323961

one can specify the argument `strata` to extract strata-specific estimates:

```
confint(BTstrata, strata = 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

⚠ The pooled estimator presented in this section has a conditional interpretation, as it summarizes comparisons made between observations from the same strata. They will generally differ from the marginal (i.e. non-adjusted) Net Treatment Benefit and tend to be more extreme (i.e. away from 0) in presence of group difference.

1.4 Standardization

When the interest lies in a marginal effect but one wish to adjust on baseline covariates to obtain more precise estimate, one should *not* restrict the comparisons between pairs of observations from the same strata. Instead one should estimate a Net Treatment Nenefit for each possible combinations of strata and pool the results (Buyse et al. (2025), chapter 9). This is what is being done when setting the argument `pool.strata` to "standardization":

```
BTstd <- BuyseTest(ffstrata, data = veteran, trace = 0, pool.strata = "standardization")
model.tables(BTstd)[,c("strata", "total", "delta", "Delta", "lower.ci", "upper.ci", "p.value")]
```

	strata	total	delta	Delta	lower.ci	upper.ci	p.value
1	global	100.000000	-0.11874500	-0.118745	-0.2857534	0.0552638	0.1805479
2	squamous	6.393862	0.21930736	NA	NA	NA	NA
3	smallcell.squamous	12.787724	0.35699653	NA	NA	NA	NA
4	adeno.squamous	3.836317	0.41018519	NA	NA	NA	NA
5	large.squamous	6.393862	0.03622106	NA	NA	NA	NA
6	squamous.smallcell	5.754476	-0.50654161	NA	NA	NA	NA
7	smallcell	11.508951	-0.17921811	NA	NA	NA	NA
8	adeno.smallcell	3.452685	-0.25308642	NA	NA	NA	NA
9	large.smallcell	5.754476	-0.80740741	NA	NA	NA	NA
10	squamous.adeno	5.754476	-0.41165224	NA	NA	NA	NA
11	smallcell.adeno	11.508951	-0.02906379	NA	NA	NA	NA
12	adeno	3.452685	-0.10339506	NA	NA	NA	NA
13	large.adeno	5.754476	-0.76311728	NA	NA	NA	NA
14	squamous.large	3.836317	-0.04494949	NA	NA	NA	NA
15	smallcell.large	7.672634	0.25946502	NA	NA	NA	NA
16	adeno.large	2.301790	0.21296296	NA	NA	NA	NA
17	large	3.836317	-0.37222222	NA	NA	NA	NA

Here `strata` equal to `squamous` means that the comparison between the active and control group was made using only patients whose lung cancer cell type were `squamous`. We retrieve the same results as when setting `pool.strata` to "buyse" or "CMH". However now additional strata have been added like "smallcell.squamous" where control patients whose lung cancer cell type were `smallcell` are being compared to active patients whose lung cancer cell type were `squamous`. Indeed:

```
BuyseTest(trt ~ tte(time, threshold = 20, status = "status"),
  data = rbind(veteran[veteran$celltype == "smallcell" & veteran$trt == "P1",],
    veteran[veteran$celltype == "squamous" & veteran$trt == "Exp",]),
  trace = 0)
```

```
endpoint threshold Delta
time          +20 0.357
```

leads, up to rounding, to the same result.

Note: it is possible to extract the strata-specific estimate (e.g. `coef(BTstd, strata = TRUE)`) but the software does not keep track of the strata-specific uncertainty via the H-decomposition and thus not able to output confidence intervals. A resampling method could be used if those are of interest:

```
BTstd.boot <- BuyseTest(ffstrata, data = veteran, trace = 0, pool.strata = "standardization",
                        method.inference = "bootstrap", n.resampling = 100, seed = 10)
confint(BTstd.boot, strata = TRUE)[1:6,]
```

Estimated p-value of 1 - consider increasing the number of bootstrap samples

	estimate	se	lower.ci	upper.ci	null	p.value
time_t20.squamous	0.21930736	0.2080541	-0.20675900	0.5739010	0	0.31000000
time_t20.smallcell.squamous	0.35699653	0.1687546	0.05407602	0.6725760	0	0.00990099
time_t20.adeno.squamous	0.41018519	0.1934063	0.02191406	0.7106061	0	0.02000000
time_t20.large.squamous	0.03622106	0.2205302	-0.36689103	0.4289194	0	1.00000000
time_t20.squamous.smallcell	-0.50654161	0.1702545	-0.80210648	-0.1179729	0	0.00990099
time_t20.smallcell	-0.17921811	0.1738337	-0.49175000	0.1397222	0	0.30000000

Here `n.resampling` was set to a low value only to save computation time but this may lead to unreliable confidence intervals/p-values: larger values are recommended (e.g. 10000).

1.5 Using multiple endpoints (hierarchical)

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 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: Exp (treatment) vs. Pl (control)
- censored pairs : probabilistic score based on the survival curves
- neutral pairs : re-analyzed using lower priority endpoints
- results

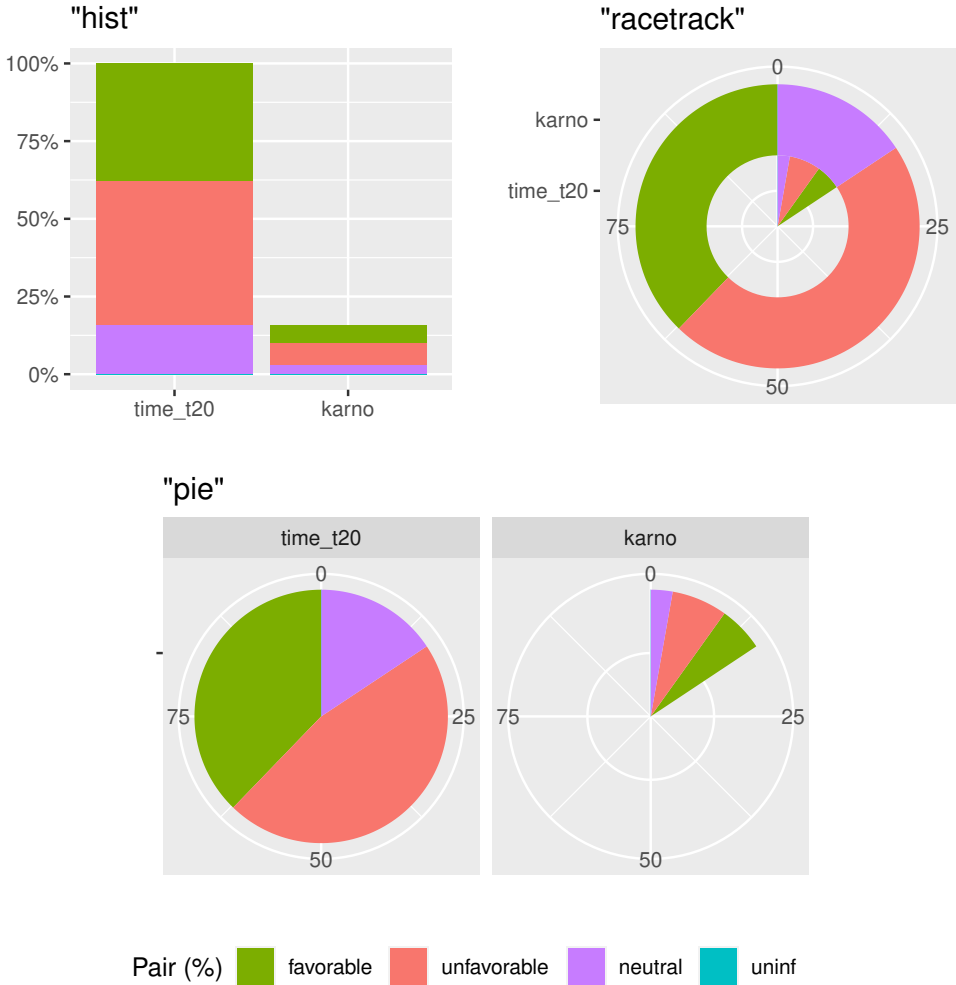
endpoint	threshold	total(%)	favorable(%)	unfavorable(%)	neutral(%)	uninf(%)	delta	Delta
time	+20	100.00	37.78	46.54	15.68	0	-0.0877	-0.0877
karno		15.68	5.78	7.11	2.78	0	-0.0133	-0.1009

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 treatment benefit for the first endpoint (line 1) and -10.09% is the net treatment 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 = "racetrack")
plot(BT.H, type = "pie")
```



⚠ As mentionned in chapter 5, section 5.5.2 of [Buyse et al. \(2025\)](#), in presence of right-censoring and when using a probabilistic scoring rule (e.g. Peron's scoring rule), the joint probability across endpoints is approximated by the product of the endpoint-specific marginal probabilities, e.g.:

$$\begin{aligned}\hat{\mathbb{P}}[Y_2 > X_2 + \tau, |X_1 - Y_1| < \tau_1] &= \hat{\mathbb{P}}[Y_2 > X_2 + \tau | |X_1 - Y_1| < \tau_1] \hat{\mathbb{P}}[|X_1 - Y_1| < \tau_1] \\ &\approx \hat{\mathbb{P}}[Y_2 > X_2 + \tau] \hat{\mathbb{P}}[|X_1 - Y_1| < \tau_1]\end{aligned}$$

When working with multiple, correlated, censored endpoints this approximation can lead to some bias. See the remainder of chapter 5 of [Buyse et al. \(2025\)](#) for a more principled estimation method that is however not yet implemented in `BuyseTest`. A point estimate could however be obtained from `BuyseTest` by providing an appropriate survival model in the `model.tte` argument.

1.6 Using multiple endpoints (non-hierarchical)

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 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: Exp (treatment) vs. Pl (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
2 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
2 -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 by applying 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

Note: the apparent discrepancy in p-value between the hierarchical and non-hierarchical GPC at the first priority (0.3762 vs 0.3698 vs 0.3707) is due to the use of a transformation that makes the p-value dependent on the estimate. Otherwise the p-value would be the same at the first priority, e.g.:

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

	estimate	se	lower.ci	upper.ci	null	p.value
time_t20	-0.07012668	0.07808721	-0.2231748	0.08292143	0	0.3691557
karno	-0.07639267	0.09093303	-0.2546181	0.10183280	0	0.4008534

1.7 Statistical inference

Uncertainty about the estimates can be quantified using:

- argument `method.inference`

- **permutation test** ("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 treatment 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**: Exp (treatment) vs. Pl (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	0.35265

- **bootstrap resampling** ("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 treatment 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**: Exp (treatment) vs. Pl (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
[-0.2721;0.1034] 0.383

- **asymptotic distribution** ("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 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: Exp (treatment) vs. Pl (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 `seed` argument is used to generate a seed for each sample. The number of samples is set using the argument `n.resampling` and it should be 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").

It is possible to relax the exchangeability assumption using a studentized permutation. A studentized bootstrap is also possible to improve on the better small samples properties of the bootstrap confidence intervals. Both rely on the asymptotic approach to estimate standard errors and are more numerically intensive.

1.8 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 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: Exp (treatment) vs. Pl (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"`, e.g.:

1.9 What about a multiplicative instead of additive threshold?

If the interest lies in $\mathbb{P}[Y \geq \tau X] - \mathbb{P}[X \geq \tau Y]$ instead of $\mathbb{P}[Y \geq X + \tau] - \mathbb{P}[X \geq Y + \tau]$ one should specify a `*` in the operator:

```
ffstar <- trt ~ tte(time, status = "status", threshold = 20, operator = "*")
BTstar <- BuyseTest(ffstar, data = veteran, trace = 0)
print(BTstar)
```

```
endpoint threshold total(%) favorable(%) unfavorable(%) neutral(%) uninf(%) Delta
time      *20      100      5.3      6.13      88.57      0 -0.0083
CI [2.5% ; 97.5%] p.value
[-0.068;0.0515] 0.78637
```

To have a multiplicative threshold when smaller values are favorable use `*<0`.

1.10 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 treatment benefit (delta: endpoint specific, Delta: global)
- 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 treatment benefit (delta: endpoint specific, Delta: global)
- 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.

1.11 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. When planning multiple GPC, summarize the results can be done via one of two principles:

- **intersection union principle:** one rejects the (global) null hypothesis if there is evidence for an effect in all the GPC analyses. This is typically a sensitivity analysis: checking that the results are not too sensitive to the choice of an hyperparameter. No multiplicity adjustment is needed other than considering the largest p-value among all tests. For instance, when checking whether the estimated net treatment benefit is similar across a range of threshold of clinical relevance, we would obtain a p-value of 0.76

```
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. This is a typical exploratory analysis where one look for the most promising outcome. Adjustment for multiplicity is needed. Since estimates from GPC procedure are typically highly correlated, one can improve on bonferroni adjustment using a max-test adjustment. This is what is performed via the `BuyseMultComp` function:

```
BuyseMultComp(BT.H, endpoint = 1:2)
```

```
- Univariate tests:
      estimate      se  lower.ci  upper.ci null  p.value lower.band upper.band
time_t20 -0.08765836 0.09760901 -0.2735301 0.10452446    0 0.371617 -0.2798817 0.1113226
karno    -0.10092285 0.09971277 -0.2901336 0.09588144    0 0.314777 -0.2965716 0.1028561
      adj.p.value
time_t20 0.4117239
karno    0.3508339
```

Here we look at whether there is a benefit in survival alone (first priority `time_t20`) or a benefit over both endpoint (second priority `karno`). Setting the argument `cumulative` to `FALSE` when considering non-hierarchical GPC analyses enables to efficiently adjust endpoint-specific GPC for multiple comparisons:

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

```
- Univariate tests:
      estimate      se  lower.ci  upper.ci null  p.value lower.band upper.band
time_t20 -0.08765836 0.09760901 -0.2735301 0.1045245    0 0.3716170 -0.2953329 0.1279261
karno    -0.03132992 0.09787113 -0.2197111 0.1593037    0 0.7490407 -0.2420777 0.1822409
      adj.p.value
time_t20 0.5597555
karno    0.9236602
```

One can also consider the global endpoint of two different GPC analyses:

```
BuyseMultComp(list(hierarchical = BT.H, Obrien = BT.nH), cluster = "id")
```

```
- Univariate tests:
      estimate      se  lower.ci  upper.ci null  p.value lower.band
hierarchical -0.10092285 0.09971277 -0.2901336 0.09588144    0 0.3147770 -0.3014645
Obrien       -0.05949414 0.08700807 -0.2266953 0.11111326    0 0.4951361 -0.2368800
      upper.band adj.p.value
hierarchical 0.1081696 0.3831444
Obrien       0.1217304 0.5851872
```

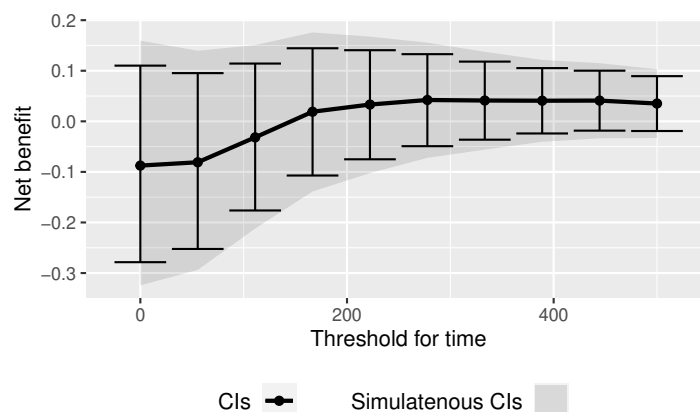
Finally the `sensitivity` method can also be used to adjust for multiple comparisons over multiple thresholds:

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

	time	estimate	lower.ci	upper.ci	p.value	lower.band	upper.band	adj.p.value
1	0.00000	-0.08752774	-0.27851884	0.11012263	0.3858177	-0.32447773	0.1597587	0.7745625
2	55.55556	-0.08095829	-0.25229456	0.09530004	0.3682107	-0.29398532	0.1397311	0.7528122
3	111.11111	-0.03170177	-0.17629003	0.11422560	0.6712414	-0.21221507	0.1509036	0.9810274
4	166.66667	0.01896964	-0.10713643	0.14447503	0.7688360	-0.13890539	0.1759043	0.9969926
5	222.22222	0.03315614	-0.07506821	0.14060850	0.5486177	-0.10248262	0.1675845	0.9257172
6	277.77778	0.04217485	-0.04914025	0.13279075	0.3653982	-0.07235302	0.1556050	0.7492675
7	333.33333	0.04112991	-0.03631838	0.11808708	0.2979105	-0.05603319	0.1375213	0.6545176
8	388.88889	0.04075638	-0.02402114	0.10519310	0.2174545	-0.04052732	0.1215042	0.5203739
9	444.44444	0.04097871	-0.01844156	0.10011054	0.1764199	-0.03358825	0.1150920	0.4429140
10	500.00000	0.03517173	-0.01915553	0.08929191	0.2044340	-0.03300243	0.1030201	0.4967546

Here by setting the argument `band` to `TRUE` (and `adj.p.value` 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. The difference can be visualized using the `autoplot` method:

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



Simultaneous and pointwise confidence intervals are here of similar width due to the very high correlation between estimates across thresholds:

```
BTse.cor <- cor(lava::iid(BTse.ustat))
range(BTse.cor[lower.tri(BTse.cor)])
```

```
[1] 0.3716902 0.9848999
```

Note that 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
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

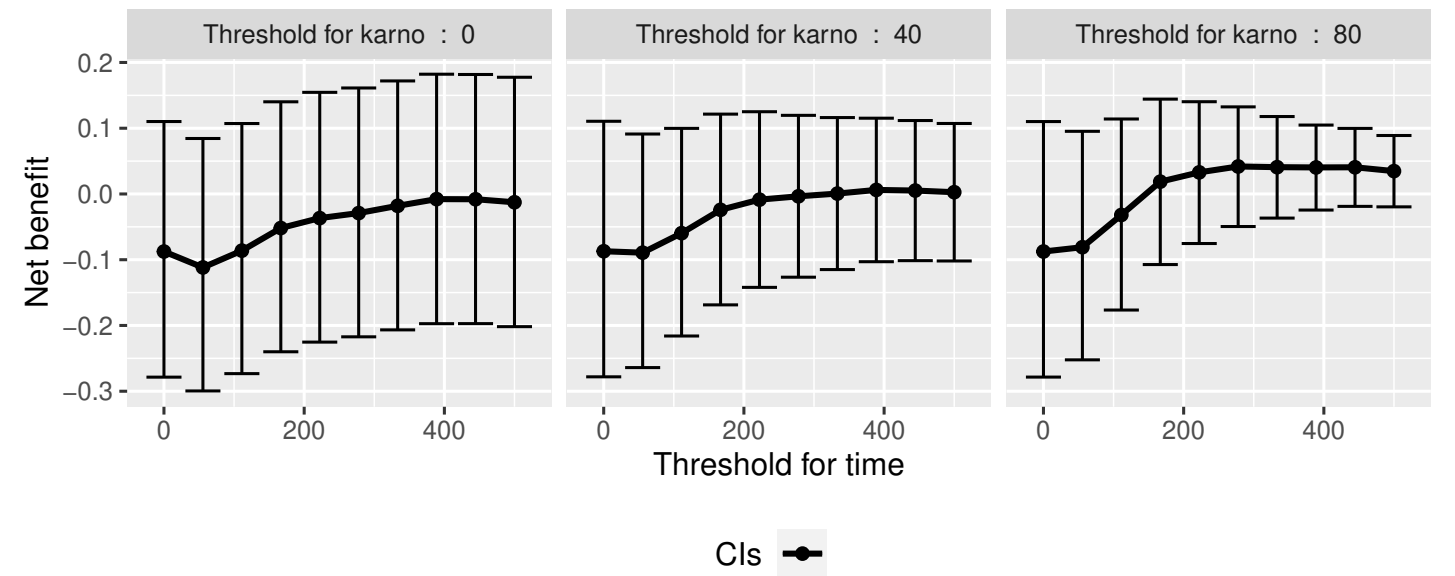
```

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))

```



The autoplot function can only be used when 1 or 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 insight 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 (long format)

The net treatment 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 in a data.frame format (one row = one pair). For instance the following code extracts the contribution for the first endpoint:

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

Key: <index.Exp, index.Pl>

	index.Pl	index.Exp	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 unfavorable 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),]
```

	id	trt	celltype	time	status	karno	diagtime	age	prior
70	70	Exp	squamous	999	1	90	12	54	10
1	1	Pl	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 treatment 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
```

2.2 Extracting the contribution of each pair to the statistic (matrix format)

It is also possible to extract the results of the comparisons in a matrix format:

```
Mscore <- getMatrixScore(BT.keep, endpoint = 1)
dim(Mscore)
Mscore[1:4,1:4]
```

```
[1] 69 68
      [,1] [,2] [,3] [,4]
[1,]    1    1 0.9600 1.0
[2,]    1   -1 -0.6304 -0.2
[3,]    1   -1 -0.0802 0.9
[4,]    1    0 0.4700 1.0
```

where the rows correspond to the 'placebo' observations and the columns to the 'experimental' observations. To obtain all possible pairwise comparisons, including within group, one can set the argument `within` to `TRUE`:

```
MscoreAll <- getMatrixScore(BT.keep, endpoint = 1, within = TRUE)
dim(MscoreAll)
```

```
[1] 137 137
      [,1] [,2] [,3] [,4]
[1,]    0    1    1    1
[2,]   -1    0   -1   -1
[3,]   -1    1    0   -1
[4,]   -1    1    1    0
```

We then obtain a squared matrix with as many row and columns as observations (Placebo and Experimental) that can be divided in 3 blocks:

- A: within 'placebo' comparisons (0 on the diagonal)
- B: across group comparisons
- C: within 'experimental' comparisons (0 on the diagonal), identical to when the argument `within` was `FALSE` (default value)

$$\begin{bmatrix} A & B \\ B^T & C \end{bmatrix}$$

```
rbind(cbind(MscoreAll[1:4,1:4],NA,MscoreAll[70:73,1:4]),
      NA,
      cbind(MscoreAll[1:4,70:73],NA,MscoreAll[70:73,70:73]))
```

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]	[,8]	[,9]
[1,]	0	1	1.0000	1.0	NA	-1.0000	-1.0000	-1.0000	-1.0000
[2,]	-1	0	-1.0000	-1.0	NA	-1.0000	1.0000	1.0000	0.0000
[3,]	-1	1	0.0000	-1.0	NA	-0.9600	0.6304	0.0802	-0.4700
[4,]	-1	1	1.0000	0.0	NA	-1.0000	0.2000	-0.9000	-1.0000
[5,]	NA	NA	NA	NA	NA	NA	NA	NA	NA
[6,]	1	1	0.9600	1.0	NA	0.0000	-1.0000	-0.9076	-0.8000
[7,]	1	-1	-0.6304	-0.2	NA	1.0000	0.0000	0.6740	1.0000
[8,]	1	-1	-0.0802	0.9	NA	0.9076	-0.6740	0.0000	0.5338
[9,]	1	0	0.4700	1.0	NA	0.8000	-1.0000	-0.5338	0.0000

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

2.3 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

```

2.3.1 Computation of the score with only one censored event

Let's look at pair 91:

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

```

Key: <index.Exp, index.Pl>
      index.Pl index.Exp indexWithinStrata.Pl indexWithinStrata.Exp favorable unfavorable
1:         22         71              22              2              0      0.6950827
      neutral uninf weight
1: 0.3049173      0      1

```

In the dataset this corresponds to:

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

```

      id trt  celltype time status karno diagtime age prior
22 22  Pl smallcell   97      0    60         5 67      0
71 71 Exp  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
```

2.3.2 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]
```

```
Key: <index.Exp, index.Pl>
      index.Pl index.Exp indexWithinStrata.Pl indexWithinStrata.Exp favorable unfavorable
1:         10         72              10              3 0.5058685    0.3770426
      neutral uninf weight
1: 0.1170889    0      1
```

which corresponds to the observations:

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

```
      id trt celltype time status karno diagtime age prior
10 10 Pl squamous  100      0   70      6  70    0
72 72 Exp 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 wrapper:

```
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, unless re-analyzed at a lower priority endpoint. 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)
```

	id	treatment	eventtimeUncensored	eventtime	status	toxicity	eta_toxicity	status1
1:	1	C	0.2135567	0.2135567	1	yes	-0.07945702	1
2:	2	C	0.3422379	0.3422379	1	no	1.18175155	1
3:	3	C	1.3933222	1.3933222	1	no	2.18614406	1
4:	4	C	0.6737702	0.1961599	0	no	0.40617493	1
5:	5	C	0.5642992	0.5642992	1	yes	-0.73835910	1
6:	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 treatment benefit estimated with the uncensored event times:

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

```
eventtimeUncensored_t0.5
-0.271
```

using the censored survival times. The `scoring.rule` argument 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 survival distribution/cumulative distribution function which, by default, will be a Kaplan Meier estimator stratified on treatment and GPC `strata` variable (if any).

- **the Efron's scoring rule** same as the Peron's scoring rule except that the survival curve is extrapolated to 0 when its tail is unknown. Only possible when using a (stratified) Kaplan-Meier estimator and no competing risks.
- **the Latta's scoring rule** same as the Peron's scoring rule except that the survival curve/ cumulative distribution function is assumed to be the same across treatment groups. Only possible when using a Kaplan-Meier estimator.
- **Parametric scoring rule** same as the Peron's scoring rule except that the survival curve is assumed to follow a parametric distribution (e.g. Exponential or Weibull). Only available when there are no competing risks. Based on `survival::survreg` which is compatible with the following distributions:

```
names(survival::survreg.distributions)
```

```
[1] "extreme"      "logistic"     "gaussian"     "weibull"      "exponential" "rayleigh"
[7] "loggaussian" "lognormal"    "loglogistic" "t"
```

Uninformative score will typically arise with the Gehan's scoring rule and, in presence of administrative censoring, with Peron's/Latta's scoring rule as the survival curve is not entirely identified. Without lower-priority endpoint this will typically bias the estimates (e.g. of the Net Treatment Benefit) towards 0⁵. As a remedie one can:

- use a **restriction time** within the time interval where the survival curve can be estimated for each group.
- use a lower priority endpoint.
- use parametric assumption in survival model to defined the survival curve over all timepoints. This can be achieved via the `model.tte` argument or using the Efron's/Weibull's/... scoring rule.
- use a proportional hazard assumption to **impute the uninformative scores**. This can be achieved via the `correction.uninf` argument 1.

The first two solutions lead to a change of estimand, the first being clearly defined while the definition of the second depends of the censoring distribution. The last two solutions correspond make instead statistical assumptions, the former assumptions being more explicit than with the later solution. The following subsection exemplify some of the previous possibilities on an illustrative dataset.

3.1 Gehan's scoring rule

In the example, Gehan's scoring rule:

```
e.Gehan <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                    data = dt, scoring.rule = "Gehan", trace = 0)
model.tables(e.Gehan)
```

⁵While the power is typically reduced, the type 1 error will typically still be controled under independent between the censoring and event of interest process, conditionally on strata variables (if any)

```

      endpoint threshold total favorable unfavorable neutral uninf   Delta   lower.ci
1 eventtime      0.5   100      4.67      14.39   20.44  60.5 -0.0972 -0.1593869
      upper.ci    p.value
1 -0.03424474 0.002514882

```

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

3.2 Latta's scoring rule

The Latta's scoring rule:

```

e.Latta <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                    data = dt, scoring.rule = "Latta", trace = 0)
model.tables(e.Latta)

```

```

      endpoint threshold total favorable unfavorable neutral uninf   Delta   lower.ci
1 eventtime      0.5   100 17.52701   36.13826 46.33473      0 -0.1861125 -0.286479
      upper.ci    p.value
1 -0.08170553 0.0005240922

```

leads to an estimate closer to the truth, but still attenuated towards 0. This is not surprising as under the alternative we 'impute' the censored pairs under the null. In this specific example there are no uninformative pairs as the observation with the largest event time was an event:

```
dt[,.SD[which.max(eventtime)]]
```

```

      id treatment eventtimeUncensored eventtime status toxicity eta_toxicity status1
1: 72          C      2.668629  2.668629      1     yes    -1.925644      1

```

In other cases, and in presence of administrative censoring, they will be uninformative pairs.

Note: this scoring rule can be 'manually' implemented by first fitting a non-parametric survival model common to both treatment groups via `prodlm`:

```

e.prodlmLatta <- prodlm(Hist(eventtime, status) ~ 1, data = dt)
attr(e.prodlmLatta,"iidNuisance") <- TRUE

```

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

```

e.LattaManual <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                          model.tte = e.prodlmLatta,
                          data = dt, scoring.rule = "Peron", trace = 0)
confint(e.LattaManual)

```

```

      estimate      se lower.ci   upper.ci null      p.value
eventtime_t0.5 -0.1861125 0.05241572 -0.286479 -0.08170553      0 0.0005240922

```

3.3 Peron's scoring rule

In the example, Peron's scoring rule:

```
e.Peron <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                     data = dt, scoring.rule = "Peron", trace = 0)
model.tables(e.Peron)
```

```
      endpoint threshold total favorable unfavorable neutral      uninf      Delta      lower.ci
1 eventtime      0.5    100   11.1737    43.33707 44.12373 1.365504 -0.3216337 -0.4584262
      upper.ci      p.value
1 -0.1699543 5.385074e-05
```

leads to an estimate quite close to the truth, despite still having some uninformative pairs (about 1.37%). Indeed the last observation in one group is a drop-out:

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

```
      treatment  id eventtimeUncensored eventtime status toxicity eta_toxicity status1
1:           C  72          2.668629  2.668629      1      yes  -1.9256436          1
2:           T 154          1.674053  1.588657      0      yes  -0.8647272          1
```

so the full survival curve could not be identified.

Note: this scoring rule can be 'manually' implemented by first fitting a non-parametric survival model specific to each treatment group via `prodlm`:

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

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

```
e.PeronManual <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                          model.tte = e.prodlmPeron,
                          data = dt, scoring.rule = "Peron", trace = 0)
confint(e.PeronManual)
```

```
      estimate      se      lower.ci      upper.ci null      p.value
eventtime_t0.5 -0.3216337 0.07403487 -0.4584262 -0.1699543  0 5.385074e-05
```

When the dataset used to fit the survival model match the one used to run the GPC procedure, the overall uncertainty will be computed. Otherwise:

```
dt2 <- dt[order(dt$eventtime)]
e.PeronManual2 <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                          model.tte = prodlm(Hist(eventtime, status) ~ treatment, data =
dt2),
                          data = dt, scoring.rule = "Peron", trace = 0)
confint(e.PeronManual2)
```

Uncertainty related to the estimation of the survival probabilities is ignored.

Consider adding an attribute "iidNuisance" to the argument 'model.tte' taking value TRUE to change

	estimate	se	lower.ci	upper.ci	null	p.value
eventtime_t0.5	-0.3216337	0.05153296	-0.4187087	-0.2172912	0	6.570106e-09

the survival probabilities will assumed to be known with infinite precision and only the uncertainty of the GPC procedure will be considered.

3.4 Efron's scoring rule

The Efron's scoring rule:

```
e.Efron <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                    data = dt, scoring.rule = "Efron", trace = 0)
model.tables(e.Efron)
```

	endpoint	threshold	total	favorable	unfavorable	neutral	uninf	Delta	lower.ci
1	eventtime	0.5	100	11.1737	43.97856	44.84774	0	-0.3280486	-0.466052
				upper.ci				p.value	
1				-0.1744621				4.871577e-05	

leads to no uninformative pairs as the survival is set to 0 after the last observation.

Note: an add-hoc modification of the data can be used to 'manually' implement this scoring rule.

Recalling that the tail of the survival curve is unknown only in the treatment group:

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

	treatment	id	eventtimeUncensored	eventtime	status	toxicity	eta_toxicity	status1
1:	C	72	2.668629	2.668629	1	yes	-1.9256436	1
2:	T	154	1.674053	1.588657	0	yes	-0.8647272	1

We can set the last censored observation(s) in that group to have the event shortly after the censoring time:

```
dtEfron <- copy(dt)
dtEfron[treatment=="T" & id == 154, c("eventtime", "status") := .(eventtime+1e-10, 1)]
## dt2[treatment=="T" & eventtime > 1.58865, status := 1]
```

Estimate the corresponding non-parametric survival model via prodlim:

```
e.prodlimEfron <- prodlim(Hist(eventtime, status) ~ treatment, data = dtEfron)
attr(e.prodlimEfron, "iidNuisance") <- TRUE
```

and run the GPC with this survival model:

```
e.Efron <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
                    model.tte = e.prodlimEfron,
                    data = dt, scoring.rule = "Peron", trace = 0)
confint(e.Efron)
```

	estimate	se	lower.ci	upper.ci	null	p.value
eventtime_t0.5	-0.3280486	0.07484093	-0.466052	-0.1744621	0	4.871577e-05

3.5 Scoring rule based on a parametric survival model

Parametric survival distribution specified in the `survreg` function of the `survival` package:

```
names(survreg.distributions)
```

```
[1] "extreme"      "logistic"     "gaussian"     "weibull"      "exponential" "rayleigh"
[7] "loggaussian" "lognormal"    "loglogistic" "t"
```

can be used to model the group-specific survival and plugged in the Peron-scoring rule formula:

```
e.Weibull <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
  data = dt, scoring.rule = "Weibull", trace = 0)
model.tables(e.Weibull)
```

```
      endpoint threshold total favorable unfavorable neutral      uninf      Delta lower.ci
1 eventtime      0.5   100  13.54196   41.34855 45.10801 0.001482627 -0.2780659 -0.4192085
      upper.ci      p.value
1 -0.1237996 0.0005138051
```

which is very close to the true value. This is not surprising since we used a parametric survival model compatible with the data generating mechanism (exponential distribution). In theory there should be no uninformative pairs. However `BuyseTest` discretise the (continuous) survival distribution into a piecewise constant distribution and the uninformative pairs corresponds to the density beyond the last discretisation point. Internally the survival curve is discretized using 1000 points starting from survival = 1 to survival = 0.001. A greater resolution can be specified with a number following the distribution name: Note: this scoring rule can be 'manually' implemented by first fitting a parametric survival model specific to each treatment group via `survreg`, e.g.:

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

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

```
e.WeibullManual <- BuyseTest(treatment ~ tte(eventtime, status, threshold = 0.5),
  model.tte = e.survregWeibull,
  data = dt, scoring.rule = "Peron", trace = 0)
model.tables(e.WeibullManual)
```

```
      endpoint threshold total favorable unfavorable neutral      uninf      Delta lower.ci
1 eventtime      0.5   100  11.65444   34.18937 54.14472 0.01147085 -0.2253494 -0.3476693
      upper.ci      p.value
1 -0.09548719 0.0007624659
```

The argument `n.grid` controls how many points are used to discretise the survival curve.

3.6 Correction via re-weighting (Péron et al., 2021)

3.6.1 At the trial level

The score of informative pairs is inflated proportionally to the amount non-informative score, e.g. as in Buyse (2008). It can be seen as right-censoring under a proportional hazard-like assumption. While this can be reasonable if there are no lower priority endpoints, it will disregard lower priority information of pairs classified uninformative at the higher priority endpoint.

⚠ The current implementation does not account for the uncertainty about the inflation factor when using `method.inference` equal to "U-statistic".

In the present example, the correction leads to an estimate:

```
BT.trialW <- 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.trialW)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net treatment benefit (delta: endpoint specific, Delta: global)
- 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
```

reasonably close to the true net treatment benefit. The correction could also be applied with Peron's scoring rule. However since there were 'only' 1.37% uninformative pair it will not substantially affect the results of this analysis. To get some inside about the correction we can look at the scores of the pairs:

```
iScore <- getPairScore(BT.trialW, 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.

3.6.2 At the pair level

This score of the uninformative pairs is set the average favorable, unfavorable, and neutral probability observed on the sample:

```
BT.pairI <- 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.pairI)
```

Generalized pairwise comparisons with 1 endpoint

```
- statistic      : net treatment benefit (delta: endpoint specific, Delta: global)
- 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
```

In the present example it leads to exactly the same result since there is only one endpoint. But in presence of multiple endpoints the neutral score of the uninformative pairs would be analysed based on the observed lower-priority endpoint of these uninformative pairs, which makes it better suited to analyze multiple endpoints. We can see the neutral score 'imputed' to each uninformative pair (line 3):

```
iScore <- getPairScore(BT.pairI, 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

which matches the proportion of favorable, unfavorable, and neutral pairs of the GPC analysis:

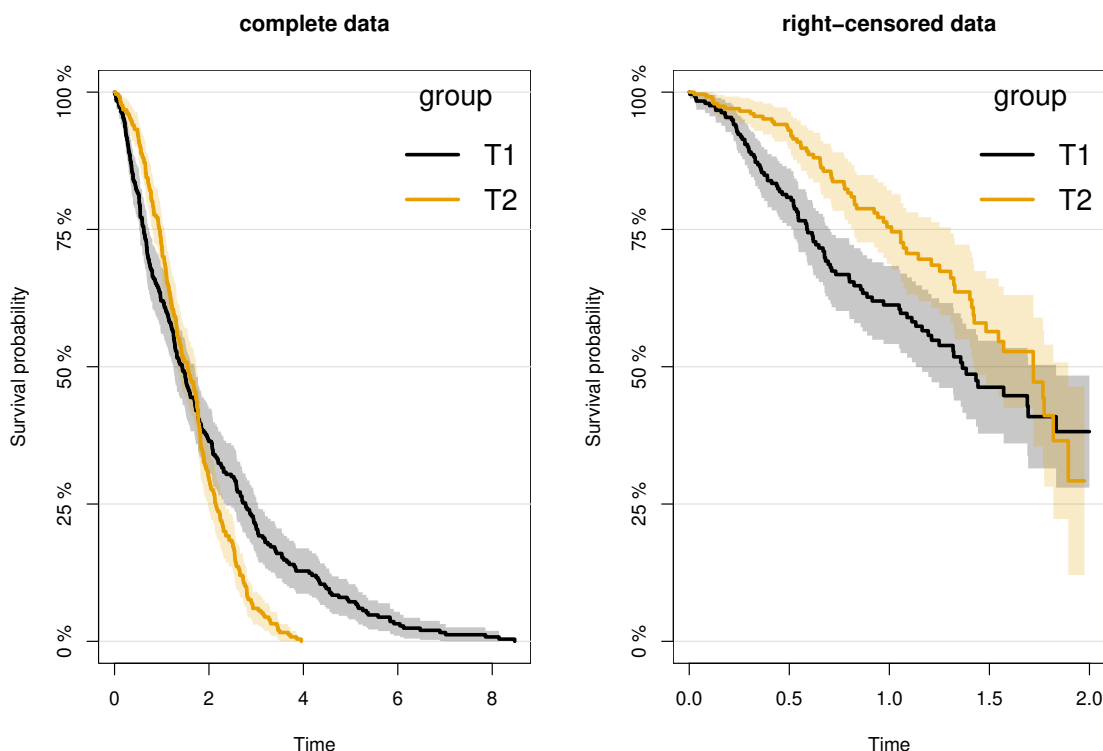
```
c(favorable = unname(coef(BT.pairI, statistic = "favorable")),
  unfavorable = unname(coef(BT.pairI, statistic = "unfavorable")),
  neutral = unname(coef(BT.pairI, statistic = "neutral")))
```

```
favorable unfavorable      neutral
0.1182278    0.3643038    0.5174684
```

3.6.3 Note on the use of the corrections

As mentioned in [Péron et al. \(2021\)](#), the corrections (at the trial or pair level) 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 treatment benefit that we would have estimated with complete data:

```
e.ref <- BuyseTest(group ~ tte(time,status), data = df, method.inference = "none",
                  trace = FALSE)
s.ref <- model.tables(e.ref, column = 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), data = df, method.inference = "none",
                          trace = FALSE, correction.uninf = 1)
s.correction <- model.tables(e.correction,
                             column = 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 <- model.tables(e.Peron, column = 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)
```

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

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

This functionality is based on the `sim` function of the `lava` package.

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))  
}  
set.seed(10)  
simFCT(101,101)
```

```
      Y group  
1:  0.02241932    0  
2: -1.07273566    0  
3:  0.76072274    0  
4: -0.25812356    0  
5:  0.97207866    0  
---  
198:  1.82349375    1  
199: -0.98560076    1  
200:  1.48143637    1  
201:  3.69314316    1  
202:  0.96244416    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 treatment benefit). We can assess the power of a test based on the net treatment 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

- net benefit statistic (null hypothesis $\Delta=0$)

endpoint	threshold	n.T	n.C	mean.estimate	sd.estimate	mean.se	rejection.rate
Y	1e-12	5	5	0.2484	0.359	0.3395	0.069
		10	10	0.2471	0.2551	0.2464	0.137
		20	20	0.2444	0.1746	0.1757	0.221
		30	30	0.243	0.1436	0.1437	0.365
		50	50	0.2438	0.1114	0.1113	0.557
		100	100	0.2458	0.0804	0.0787	0.865

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 an approximate sample size satisfying a specific type 1 and type 2 error rate:

```
nW <- powerBuyseTest(sim = simFCT, method.inference = "u-statistic",
  power = 0.8, max.sample.size = 1000,
  formula = group ~ cont(Y), null = c("netBenefit" = 0),
  n.rep = c(1000,10), seed = 10, cpus = 5, trace = 0)
```

This procedure is inspired from the procedure presented by [Brunner et al. \(2018\)](#) in section 3.8.2.2. In short, several 'large' datasets are generated and analyzed using GPC to approximate the statistic of interest (Δ) and its asymptotic variance (σ^2). The sample size needed to achieve the requested power ($1 - \beta$) and the requested type 1 error (α) is then deduced, given a dataset, according to the equation $N = \sigma^2 \frac{(u_{1-\alpha/2} + u_{1-\beta})^2}{\Delta^2}$ where u_x denotes the x-quantile of the normal distribution. The estimated sample size is then the average calculated sample size across dataset. The argument `max.sample.size` specifies the number of observation per group in the 'large' dataset (here 1000 per group) and the second element of the argument `n.rep` specifies the number of datasets (here 10). The quality of the approximation, as well as the computation time, thus improves when increasing `max.sample.size` and `n.rep`[2]. The achieved power with the estimated sample size can be output as usual using the `summary` method:

```
summary(nW)
```

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]): 89 [60;145] controls
                                         89 [60;145] 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  89  89          0.2452          0.0854  0.0834          0.806

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)

```

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 treatment benefit (delta: endpoint specific, Delta: global)
- 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)
```

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