Performing GPC with repeated measurements

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This vignette describes how to use Generalized Pairwise comparisons (GPC) in a design where each subject undergo several measurements. Traditional GPC assumes independent observations which is likely not the case in such design since observations from the same subject are typically correlated. This is an area of development for the BuyseTest package so the content of this vignette may change in newer versions.

1 Paired design

The Diabetic Retinopathy Study (DRS), which data is available from R package survival, included 197 patients who had one of their eye randomized to laser treatment while the other did not receive any treatment:

```
data(diabetic, package = "survival")
head(diabetic)
```

```
  id laser age   eye trt risk  time status
1  5 argon  28  left   0    9 46.23      0
2  5 argon  28 right   1    9 46.23      0
3 14 xenon  12  left   1    8 42.50      0
4 14 xenon  12 right   0    6 31.30      1
5 16 xenon   9  left   1   11 42.27      0
6 16 xenon   9 right   0   11 42.27      0
```

The outcome was time to blindness (visual acuity drop below a certain threshold). In the real study `status` equal to 0 mixes death and censoring (due to drop-out or end of study) but this complication will be neglected here for simplicity.

We will replicate some of the analyzes presented in Matsouaka (2022). In this paper they split the dataset into juvenile and adult patients:

```
diabetic$juvenile <- diabetic$age <= 19
library(LMMstar)
summarize(age ~ juvenile, data = diabetic[!duplicated(diabetic$id),])
```

```
  juvenile observed missing     mean        sd min q1 median    q3 max
1    FALSE       83       0 35.30120 11.242054  20 25     34 45.00  58
2     TRUE      114       0 10.21053  4.713892   1  7     10 13.75  19
```

and we will focus on the juvenile patients:

```
diabeticJ <- diabetic[diabetic$juvenile,]
```

1.1 Wald methods (Gehan scoring rule)

To mimic the methodology underlying the results presented in Table 1 of Matsouaka (2022), we perform GPC stratified by patient using the Gehan scoring rule:

```
library(BuyseTest)
e.BTjuv <- BuyseTest(trt ~ tte(time,status) + strata(id, match = TRUE),
                     data = diabeticJ, trace = FALSE,
                     scoring.rule =  "Gehan")
model.tables(e.BTjuv, percentage = FALSE)
```

```
  endpoint total favorable unfavorable neutral uninf     Delta   lower.ci  upper.ci    p.value
1     time   114        39          21       3    51 0.1578947 0.02591623 0.2844633 0.01922741
```

Indeed this scoring rule does not involve any extra-modeling, only evaluating the patient specific net benefit and averaging them:

```
mean(coef(e.BTjuv, strata = TRUE))
```

```
[1] 0.1578947
```

Matsouaka (2022) propose to estimate the standard error as:

```
N <- nobs(e.BTjuv)["pairs"]
pw <- coef(e.BTjuv, statistic = "favorable")
pl <- coef(e.BTjuv, statistic = "unfavorable")
sqrt((pw + pl - (pw - pl)^2)/N)
```

```
      time
0.06631828
```

which matches what `BuyseTest` output:

```
confint(e.BTjuv)
```

```
      estimate         se   lower.ci  upper.ci null    p.value
time 0.1578947 0.06631828 0.02591623 0.2844633    0 0.01922741
```

By default `confint` uses a hyperbolic tangent to compute confidence intervals (CIs), which will then differ from the 'Wald' discussed in Matsouaka (2022). These 'untransformed Wald' CIs can be retrieved by setting the argument `transform` to `FALSE`:

```
confint(e.BTjuv, transform = FALSE)
```

```
      estimate         se   lower.ci  upper.ci null    p.value
time 0.1578947 0.06631828 0.02791329 0.2878762    0 0.01727214
```

Note: naively one may think to estimate the standard error as:

```
sqrt(var(coef(e.BTjuv, strata = TRUE))/N)
```

```
     pairs
0.06661108
```

This is equivalent (in large samples to the previous formula). Indeed:

$$
\begin{aligned}
&\mathbb{P}\left[X > Y\right] + \mathbb{P}\left[Y > X\right] - \left(\mathbb{P}\left[X > Y\right] - \mathbb{P}\left[Y > X\right]\right)^2 \\
=&\mathbb{P}\left[X > Y\right] + \mathbb{P}\left[Y > X\right] - \mathbb{P}\left[X > Y\right]^- \mathbb{P}\left[Y > X\right]^2 + 2\mathbb{P}\left[X > Y\right]\mathbb{P}\left[Y > X\right] \\
=&\mathbb{P}\left[X > Y\right](1 - \mathbb{P}\left[X > Y\right]) + \mathbb{P}\left[Y > X\right](1 - \mathbb{P}\left[Y > X\right]) + 2\mathbb{P}\left[X > Y\right]\mathbb{P}\left[Y > X\right] \\
=&\mathbb{P}\left[X > Y\right](1 - \mathbb{P}\left[X > Y\right]) + \mathbb{P}\left[Y > X\right](1 - \mathbb{P}\left[Y > X\right]) \\
&- 2(0 - \mathbb{P}\left[X > Y\right]\mathbb{P}\left[Y > X\right] - \mathbb{P}\left[X > Y\right]\mathbb{P}\left[Y > X\right] + \mathbb{P}\left[X > Y\right]\mathbb{P}\left[Y > X\right] \\
=&\mathbb{V}ar\left[\mathbb{1}_{X>Y}\right] + \mathbb{V}ar\left[\mathbb{1}_{X<Y}\right] - 2\mathbb{C}ov\left(\mathbb{1}_{X>Y}, \mathbb{1}_{X<Y}\right) \\
=&\mathbb{V}ar\left[\mathbb{1}_{X>Y} - \mathbb{1}_{X<Y}\right]
\end{aligned}
$$

There is only a factor `N/(N-1)` difference between the two:

```
sqrt(var(coef(e.BTjuv, strata = TRUE))/N) * sqrt((N-1)/N)
```

```
     pairs
0.06631828
```

1.2 MOVER method (Gehan scoring rule)

The method recommended by Matsouaka (2022) is the MOVER approach, which has been developped for a binary scoring rule (e.g. Gehan). An experimental function with the same name has been implemented in the BuyseTest package:

```
BuyseTest:::mover(e.BTjuv)
```

```
  estimate      lower      upper     pvalue
0.15789474 0.02540421 0.28317729 0.01967878
```

leading to the same results as those of the table 1 in the original article, up to rounding.

1.3 Wald methods (Peron scoring rule)

To better account for censoring one could use the Peron scoring rule where the survival is estimated across all subjects within a treatment group. One has to specify the survival model, otherwise, the BuyseTest function will estimate a treatmnet and strata specific survival curve which is impossible to perform here. The `model.tte` argument can be used to specify such survival model:

```
library(prodlim)
e.BTjuv2 <- BuyseTest(trt ~ tte(time,status) + strata(id, match = TRUE),
                      data = diabeticJ, trace = FALSE,
                      model.tte = prodlim(Hist(time,status)~ trt, data = diabeticJ))
model.tables(e.BTjuv2, percentage = FALSE)
```

```
  endpoint total favorable unfavorable neutral    uninf    Delta   lower.ci  upper.ci
1     time   114  47.36525    24.29552       3 39.33923 0.202366 0.05045454 0.3451254
      p.value
1 0.009329589
```

Ignoring the uncertainty of the survival model, the standard would be:

```
c(sqrt(var(coef(e.BTjuv2, strata = TRUE))/N),
  sqrt(var(coef(e.BTjuv2, strata = TRUE))/N) * sqrt((N-1)/N)
  )
```

```
     pairs      pairs
0.06595510 0.06566518
```

depending on whether a small sample correction is used or not. This matches the output of `BuyseTest` when ignoring the uncertainty of the survival model:

```
model.tte <- prodlim(Hist(time,status)~ trt, data = diabeticJ)
attr(model.tte, "iidNuisance") <- FALSE
confint(BuyseTest(trt ~ tte(time,status) + strata(id, match = TRUE),
                  data = diabeticJ, trace = FALSE,
                  model.tte = model.tte))
```

```
     estimate         se   lower.ci  upper.ci null     p.value
time 0.202366 0.06566518 0.07088227 0.3269375    0 0.002726979
```

⚠ Because the pairwise win and loss score are no more binary, the previous formula no more simplifies into the formula presented in Matsouaka (2022):

```
pw.peron <- coef(e.BTjuv2, statistic = "favorable")
pl.peron <- coef(e.BTjuv2, statistic = "unfavorable")
sqrt((pw.peron + pl.peron - (pw.peron - pl.peron)^2)/N)
```

```
      time
0.07179718
```

To account for the uncertainty of the survival model, BuyseTest outputs a slightly higher standard error:

```
confint(e.BTjuv2)
```

```
     estimate         se   lower.ci  upper.ci null     p.value
time 0.202366 0.07569815 0.05045454 0.3451254    0 0.009329589
```

This is achieved by considering two sources of uncertainty:

- average of a finite number of pairs:

```
pw.peronS <- coef(e.BTjuv2, statistic = "favorable", strata = TRUE)
pl.peronS <- coef(e.BTjuv2, statistic = "unfavorable", strata = TRUE)
Hterm1 <- (pw.peronS - pl.peronS) - (pw.peron - pl.peron)
```

- propage the uncertainty of the survival model to the net benefit. Because each pair appear twice (control and treatment) the impact of removing a pair on the net benefit is stored in the control and the treated is set to 0:

```
Hterm2.obs <- e.BTjuv2@iidNuisance$favorable - e.BTjuv2@iidNuisance$unfavorable
Hterm2.pair <- Hterm2.obs[diabeticJ$trt==0]
table(Hterm2.obs[diabeticJ$trt==1])
```

```
  0 
114 
```

After rescaling the terms by a factor N (number of pairs, to account for the pooling) we retrieve the uncertainty output by BuyseTest:

```
c(average = sqrt(crossprod((Hterm1/N))),
  nuisance = sqrt(crossprod((Hterm2.pair/N))),
  all = sqrt(crossprod((Hterm1/N + Hterm2.pair/N))))
```

```
   average   nuisance        all 
0.06566518 0.02084622 0.07569815
```

2 Multiple cross-over design

A more complex design is a cross-over where each patient may repeteadly experience each treatment. As an example, we will consider the PROFIL trial whose dataset is available in the BuyseTest package:

```
data(profil, package = "BuyseTest")
profil <- profil[order(profil$id),]
profil[profil$id==1 & profil$period==1,]
```

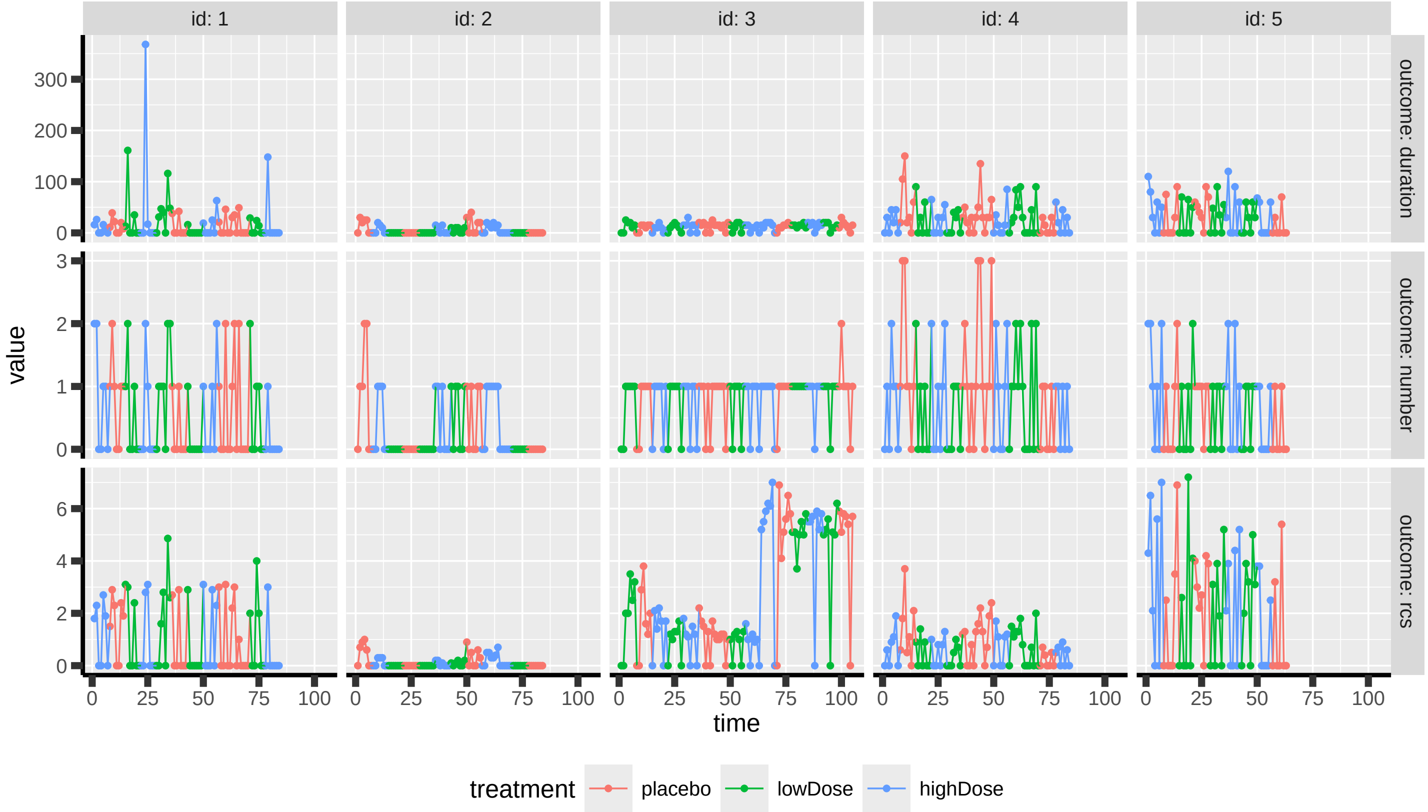
```
   id age male period time treatment rcs number duration
1   1  23    0      1    1  highDose 1.8      2       16
2   1  23    0      1    2  highDose 2.3      2       26
3   1  23    0      1    3  highDose 0.0      0        0
4   1  23    0      1    4  highDose 0.0      0        0
5   1  23    0      1    5  highDose 2.7      1       16
6   1  23    0      1    6  highDose 1.9      1       10
7   1  23    0      1    7  highDose 0.0      0        0
8   1  23    0      1    8   placebo 1.5      1       11
9   1  23    0      1    9   placebo 2.9      2       39
10  1  23    0      1   10   placebo 2.3      1       22
11  1  23    0      1   11   placebo 0.0      0        0
12  1  23    0      1   12   placebo 0.0      0        0
13  1  23    0      1   13   placebo 2.4      1       20
14  1  23    0      1   14   placebo 1.9      1        8
15  1  23    0      1   15   lowDose 3.1      1       13
16  1  23    0      1   16   lowDose 3.0      2      161
17  1  23    0      1   17   lowDose 0.0      0        0
18  1  23    0      1   18   lowDose 0.0      0        0
19  1  23    0      1   19   lowDose 2.4      1       35
20  1  23    0      1   20   lowDose 0.0      0        0
21  1  23    0      1   21   lowDose 0.0      0        0
```

The software output displays the information of the first patient relative to the first period (out of 4) during which the patient is sequentially assigned one of three treatments and her outcomes (`rcs`, `number`, and `duration`) are monitored daily. To obtain a graphical display of the outcomes over time we first reshape the data:

```
profil.L <- reshape(profil, direction = "long", idvar = c("id","time"),
                    varying = c("rcs","number","duration"), v.names = "value",
                    timevar = "outcome", times = c("rcs","number","duration"))
```

and make a spaghetti plot for the first 5 patients:

```
ggRCS <- ggplot(profil.L[profil.L$id %in% 1:5,],
                aes(x = time, group = id, color = treatment, y = value))
ggRCS <- ggRCS + geom_point() + geom_line()
ggRCS <- ggRCS + facet_grid(outcome~id, labeller = label_both, scales = "free_y")
ggRCS <- ggRCS + labs(y="")
ggRCS
```



2.1 With 2 treatment groups

Since `BuyseTest` can only handle two treatment group, we restrict the dataset to placebo and low dose:

```
lowProfil <- profil[profil$treatment %in% c("placebo","lowDose"),]
lowProfil$treatment <- droplevels(lowProfil$treatment)
```

We will use the following hierarchy and threshold of clinical relevance:

```
fff <- treatment ~ cont(rcs, threshold = 1.45, operator = "<0") + cont(number, threshold =
    0.35, operator = "<0") + cont(duration, threshold = 3, operator = "<0")
```

One could either run a separate GPC for each patient:

```
ls.lowGPC <- by(lowProfil, lowProfil$id, BuyseTest, formula = fff, trace = FALSE)
df.lowGPC <- data.frame(do.call(rbind,lapply(ls.lowGPC, coef)),
                        do.call(rbind,lapply(ls.lowGPC, nobs)),
                        Buyse = as.numeric(NA), CMH = as.numeric(NA))
df.lowGPC$Buyse <- with(df.lowGPC, pairs/sum(pairs))
df.lowGPC$CMH <- with(df.lowGPC, (pairs/(placebo+lowDose))/sum(pairs/(placebo+lowDose)))
head(df.lowGPC)
```

```
     rcs_t1.45 number_t0.35  duration_t3 placebo lowDose pairs      Buyse       CMH
1 -0.016581633 -0.015306122 -0.021683673      28      28   784 0.04694049 0.0364368
2  0.000000000  0.153061224  0.183673469      28      28   784 0.04694049 0.0364368
3 -0.001632653  0.003265306 -0.008979592      35      35  1225 0.07334451 0.0455460
4  0.117346939  0.225765306  0.154336735      28      28   784 0.04694049 0.0364368
```

```
5 -0.043083900 -0.047619048 -0.029478458      21      21    441 0.02640402 0.0273276
6  0.102040816  0.092970522  0.077097506      21      21    441 0.02640402 0.0273276
```

and pool the patient-specific Net Treatment Benefits. Different weighting scheme are possible, e.g. same weight for all patients, weight dependent on the number of blocks experienced by the patient:

```
rbind(average = colMeans(df.lowGPC[,1:3]),
      Buyse = apply(df.lowGPC[,1:3], 2, weighted.mean, w = df.lowGPC$Buyse),
      CMH = apply(df.lowGPC[,1:3], 2, weighted.mean, w = df.lowGPC$CMH))
```

```
         rcs_t1.45 number_t0.35 duration_t3
average 0.02741742   0.02755903  0.03397497
Buyse   0.01628547   0.03730092  0.04215064
CMH     0.02145018   0.03266743  0.03869945
```

This can be replicated using a single call to BuyseTest specifying a strata in the formula:

```
lowGPC <- BuyseTest(update(fff, . ~ . + strata(id, match = TRUE)),
                    data = lowProfil, trace = FALSE)
confint(lowGPC)
```

```
               estimate         se    lower.ci   upper.ci null   p.value
rcs_t1.45    0.02741742 0.02047690 -0.01273920 0.06748574    0 0.1808076
number_t0.35 0.02755903 0.03139999 -0.03401048 0.08892015    0 0.3803606
duration_t3  0.03397497 0.02801978 -0.02099009 0.08873527    0 0.2256649
```

By default, equal weights are given to each patient but other weighting schemes can be used by specifying the pool.strata argument:

```
lowGPC_Buyse <- BuyseTest(update(fff, . ~ . + strata(id, match = TRUE)),
                          data = lowProfil, pool.strata = "Buyse", trace = FALSE)
confint(lowGPC_Buyse)
```

```
               estimate         se     lower.ci   upper.ci null    p.value
rcs_t1.45    0.01628547 0.01771680 -0.018444486 0.05097618    0 0.35807018
number_t0.35 0.03730092 0.02668638 -0.015057839 0.08945568    0 0.16257765
duration_t3  0.04215064 0.02400508 -0.004957166 0.08907178    0 0.07946061
```

```
lowGPC_CMH <- BuyseTest(update(fff, . ~ . + strata(id, match = TRUE)),
                        data = lowProfil, pool.strata = "CMH", trace = FALSE)
confint(lowGPC_CMH)
```

```
               estimate         se    lower.ci   upper.ci null   p.value
rcs_t1.45    0.02145018 0.01855984 -0.01493878 0.05778241    0 0.2479363
number_t0.35 0.03266743 0.02784903 -0.02195881 0.08709921    0 0.2411232
duration_t3  0.03869945 0.02491698 -0.01019050 0.08740482    0 0.1207617
```

In term of uncertainty quantification, it is important to specify `match=TRUE` when using a single call so `BuyseTest` does not treat each line of the dataset as an independent replicate. An intuitive way to evaluate the standard error of the pooled estimator is to use the across subject variability:

```
sqrt(apply(df.lowGPC[,1:3],2,var)/NROW(df.lowGPC))
```

```
 rcs_t1.45 number_t0.35  duration_t3
0.02075177   0.03182148   0.02839590
```

This is, up to a factor `N/(N-1)` exactly what the single call approach returns. Actually we can retrieve this value by modifying the default options:

```
BuyseTest.options(order.Hprojection = 2)
lowGPC2 <- BuyseTest(update(fff, . ~ . + strata(id, match = TRUE)),
                     data = lowProfil, trace = FALSE)
confint(lowGPC2)
```

```
estimate         se    lower.ci   upper.ci null    p.value
rcs_t1.45    0.02741742 0.02075177 -0.01327825 0.06802241    0 0.1866527
number_t0.35 0.02755903 0.03182148 -0.03483625 0.08974030    0 0.3867027
duration_t3  0.03397497 0.02839590 -0.02172779 0.08946745    0 0.2318709
```

Similarly when using other weighting scheme. For instance we can retrieve the results of the Buyse pooling scheme doing:

```
df.lowGPC_center <- sweep(df.lowGPC[,1:3], MARGIN = 2, FUN = "-", STATS = coef(lowGPC_Buyse))
df.lowGPC_Wcenter <- sweep(df.lowGPC_center, MARGIN = 1, FUN = "*", STATS = df.lowGPC$Buyse)
sqrt(colSums(df.lowGPC_Wcenter^2))
```

```
rcs_t1.45 number_t0.35  duration_t3
  0.01771680   0.02668638   0.02400508
```

2.2 Accounting for time (WORK IN PROGRESS!)

In previous approaches, all pairwise comparisons are performed within each patient, not only within-block comparisons. As of version 3.3.3. it is not yet possible to match at the patient-level and only perform comparisons within the same period. One would have to perform a separate GPC for each patient, with period as a strata variable:

```
ls.lowGPC_period <- by(lowProfil, lowProfil$id, BuyseTest,
                       formula = update(fff,.~.+strata(period)), trace = FALSE)
```

We can check that fewer pairs were made thanks to stratification:

```
rbind(noStrata = nobs(ls.lowGPC[[1]]),
      PeriodStrata = nobs(ls.lowGPC_period[[1]]))
```

```
             placebo lowDose pairs
noStrata          28      28   784
PeriodStrata      28      28   196
```

In particular 49 pairs where made in each period:

```
nobs(ls.lowGPC_period[[1]],strata=TRUE)
```

```
  placebo lowDose pairs
1       7       7    49
2       7       7    49
3       7       7    49
4       7       7    49
```

One would then combine the results in a single data.frame:

```
df.lowGPC_period <- data.frame(do.call(rbind,lapply(ls.lowGPC_period, coef)),
                               do.call(rbind,lapply(ls.lowGPC_period, nobs)),
                               Buyse = as.numeric(NA), CMH = as.numeric(NA))
df.lowGPC_period$Buyse <- with(df.lowGPC_period, pairs/sum(pairs))
df.lowGPC_period$CMH <- with(df.lowGPC_period, (pairs/(placebo+lowDose))/sum(pairs/(placebo+
   lowDose)))
```

and decide on a weighting scheme to pool the results:

```
rbind(average = colMeans(df.lowGPC_period[,1:3]),
      Buyse = apply(df.lowGPC_period[,1:3], 2, weighted.mean, w = df.lowGPC_period$Buyse),
      CMH = apply(df.lowGPC_period[,1:3], 2, weighted.mean, w = df.lowGPC_period$CMH))
```

```
         rcs_t1.45 number_t0.35 duration_t3
average 0.02338177   0.03351172  0.04072124
Buyse   0.01731834   0.04085114  0.04858818
CMH     0.02333549   0.03361112  0.04077570
```

Resampling methods like a non-parametric bootstrap can then be used to quantify uncertainty and obtain confidence intervals and p-values.

2.3 With 3 or more treatment groups (WORK IN PROGRESS!)

Handling more than two treatment groups is still an area of development for the BuyseTest package. Several approaches have been proposed in the litterature and here we focus on one that aim at handling the non-transitivity issues that comes with Wilcoxon-like tests (Lumley and Gillen, 2016). This approach compare the treatment-specific distribution to a pooled distribution over all treatment groups (Thangavelu and Brunner, 2007):

```
CasinoTest(update(fff, . ~ . + strata(id)), data = profil,
           method.inference = "none", type = "unweighted")
## do not trust inference since it would require accounting for matching
```

```
                   endpoint treatment     estimate se lower.ci upper.ci null p.value
placebo: rcs            rcs   placebo -0.012193158 NA       NA       NA   NA      NA
lowDose: rcs            rcs   lowDose  0.008015351 NA       NA       NA   NA      NA
highDose: rcs           rcs  highDose  0.004177807 NA       NA       NA   NA      NA
placebo: number      number   placebo -0.020434169 NA       NA       NA   NA      NA
lowDose: number      number   lowDose  0.011566310 NA       NA       NA   NA      NA
highDose: number     number  highDose  0.008867860 NA       NA       NA   NA      NA
placebo: duration  duration   placebo -0.024148505 NA       NA       NA   NA      NA
lowDose: duration  duration   lowDose  0.013113939 NA       NA       NA   NA      NA
highDose: duration duration  highDose  0.011034566 NA       NA       NA   NA      NA
```

Its main drawback is that the assessment of say `placebo` vs. `lowDose` is now influenced by `highDose`.

References

Lumley, T. and Gillen, D. L. (2016). Characterising transitive two-sample tests. *Statistics & Probability Letters*, 109:118–123.

Matsouaka, R. A. (2022). Robust statistical inference for matched win statistics. *Statistical Methods in Medical Research*, 31(8):1423–1438.

Thangavelu, K. and Brunner, E. (2007). Wilcoxon–mann–whitney test for stratified samples and efron's paradox dice. *Journal of Statistical Planning and Inference*, 137(3):720–737.