Example 3

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```
library(corrTests)
```

Example 3. JAVELIN-100 Study

JAVELIN-100 (Powles et al 2020) is a phase 3 study of maintenance therapy for advanced or metastatic urothelial carcinoma. The dual primary endpoints are OS in PD-L1+ population (H_A) and overall population (H_B). Subjects were equally randomized to receive best supportive care (BSC) with or without avelumab (N = 350 for each group). The randomization was stratified by best response to first line chemotherapy (CR or PR vs SD) and metastatic site (visceral vs non-visceral) at the time of initiating first-line chemotherapy, but not by PD-L1 status. Among subjects with evaluable tissue samples, 189 patients in the avelumab group and in 169 in the control group are PD-L1 positive. The primary analysis of the overall population is not stratified by PD-L1 status. Among PD-L1 positive subjects, 53% subjects were randomized to avelumab plus BSC group ($r_{PD-L1+} = 0.53$). Among the subjects not PD-L1 positive, 47% subjects were randomized to avelumab plus BSC group ($r_{notPD-L1+} = 0.47$). Among all subjects in overall population, 51% subjects are in PD-L1 positive population ($\gamma = 0.51$). One interim analysis was performed with 143 events in PD-L1+ subgroup and 324 events in overall population after the study is fully enrolled.

Several strategies of improving the rejection boundaries are calculated below.

Equal Allocation: $\epsilon_{11} = \epsilon_{21}$, and $\epsilon_{12} = \epsilon_{22}$

```
jv100a = corrBounds(sf=list(sfuA=gsDesign::sfLDOF, sfuB=gsDesign::sfLDOF),  eAandB = c(143, 219), eAnot

jv100a
```

```
## $overall.alpha
##   FW.alpha alphaA alphaB side
## 1    0.025   0.01  0.015    1
##
## $bd
##     timingA incr.alphaA  cum.alphaA       bd.pA0   bd.zA0      epsA        bd.pA
## 1 0.652968 0.001434323 0.001434323 0.001434323 2.981474 1.113098 0.001596542
## 2 1.000000 0.008565677 0.010000000 0.009539308 2.343991 1.186165 0.011315197
##       bd.zA    timingB incr.alphaB  cum.alphaB       bd.pB0   bd.zB0      epsB
## 1 2.948511 0.7623529 0.005339234 0.005339234 0.005339234 2.553048 1.113098
## 2 2.279617 1.0000000 0.009660766 0.015000000 0.013387788 2.214774 1.186165
##         bd.pB     bd.zB
## 1 0.005943091 2.515505
## 2 0.015880130 2.147415
```

```
## 
## $max.eps
##   max.epsA max.epsB
## 1 1.677522 1.133711
## 2 1.443977 1.307930
## 
## $corr
##             [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.7686183 0.8080644 0.6711023
## [2,] 0.7686183 1.0000000 0.6210930 0.8731283
## [3,] 0.8080644 0.6210930 1.0000000 0.7113423
## [4,] 0.6711023 0.8731283 0.7113423 1.0000000
## 
## $cov
##            [,1]     [,2]     [,3]      [,4]
## [1,] 35.63842 41.29642 35.63842   41.29642
## [2,] 41.29642 81.00000 41.29642   81.00000
## [3,] 35.63842 41.29642 54.57913   54.16969
## [4,] 41.29642 81.00000 54.16969  106.25000
## 
## $method
## [1] "Customized Allocation"
## 
## $strat
## [1] "N"
```

Improve the overall population only: $\epsilon_{11} = \epsilon_{12} = 1$

```
jv100b = corrBounds(sf=list(sfuA=gsDesign::sfLDOF, sfuB=gsDesign::sfLDOF),  eAandB = c(143, 219), eAnotl

jv100b
```

```
## $overall.alpha
##   FW.alpha alphaA alphaB side
## 1    0.025   0.01  0.015    1
## 
## $bd
##     timingA incr.alphaA  cum.alphaA       bd.pA0    bd.zA0 epsA        bd.pA
## 1 0.652968 0.001434323 0.001434323 0.001434323 2.981474    1 0.001434323
## 2 1.000000 0.008565677 0.010000000 0.009539308 2.343991    1 0.009539308
##      bd.zA   timingB incr.alphaB  cum.alphaB       bd.pB0   bd.zB0     epsB
## 1 2.981474 0.7623529 0.005339234 0.005339234 0.005339234 2.553048 1.133711
## 2 2.343991 1.0000000 0.009660766 0.015000000 0.013387788 2.214774 1.307605
##         bd.pB    bd.zB
## 1 0.006053149 2.509031
## 2 0.017505943 2.108221
## 
## $max.eps
##   max.epsA max.epsB
## 1 1.677522 1.133711
## 2 1.444325 1.307417
## 
```

```
## $corr
##           [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.7686183 0.8080644 0.6711023
## [2,] 0.7686183 1.0000000 0.6210930 0.8731283
## [3,] 0.8080644 0.6210930 1.0000000 0.7113423
## [4,] 0.6711023 0.8731283 0.7113423 1.0000000
##
## $cov
##           [,1]      [,2]      [,3]       [,4]
## [1,] 35.63842 41.29642 35.63842   41.29642
## [2,] 41.29642 81.00000 41.29642   81.00000
## [3,] 35.63842 41.29642 54.57913   54.16969
## [4,] 41.29642 81.00000 54.16969  106.25000
##
## $method
## [1] "Customized Allocation"
##
## $strat
## [1] "N"
```

Improve the PD-L1+ only: $\epsilon_{21} = \epsilon_{22} = 1$

```
jv100c = corrBounds(sf=list(sfuA=gsDesign::sfLDOF, sfuB=gsDesign::sfLDOF),  eAandB = c(143, 219), eAnotl

jv100c
```

```
## $overall.alpha
##   FW.alpha alphaA alphaB side
## 1    0.025   0.01  0.015    1
##
## $bd
##    timingA incr.alphaA cum.alphaA      bd.pA0    bd.zA0      epsA       bd.pA
## 1 0.652968 0.001434323 0.001434323 0.001434323 2.981474 1.677522 0.002406108
## 2 1.000000 0.008565677 0.010000000 0.009539308 2.343991 1.445174 0.013785960
##      bd.zA    timingB incr.alphaB  cum.alphaB      bd.pB0    bd.zB0 epsB
## 1 2.819342 0.7623529 0.005339234 0.005339234 0.005339234 2.553048    1
## 2 2.203324 1.0000000 0.009660766 0.015000000 0.013387788 2.214774    1
##        bd.pB      bd.zB
## 1 0.005339234 2.553048
## 2 0.013387788 2.214774
##
## $max.eps
##   max.epsA max.epsB
## 1 1.677522 1.133711
## 2 1.443394 1.307912
##
## $corr
##           [,1]      [,2]      [,3]      [,4]
## [1,] 1.0000000 0.7686183 0.8080644 0.6711023
## [2,] 0.7686183 1.0000000 0.6210930 0.8731283
## [3,] 0.8080644 0.6210930 1.0000000 0.7113423
## [4,] 0.6711023 0.8731283 0.7113423 1.0000000
```

```
## 
## $cov
##          [,1]     [,2]     [,3]      [,4]
## [1,] 35.63842 41.29642 35.63842  41.29642
## [2,] 41.29642 81.00000 41.29642  81.00000
## [3,] 35.63842 41.29642 54.57913  54.16969
## [4,] 41.29642 81.00000 54.16969 106.25000
## 
## $method
## [1] "Customized Allocation"
## 
## $strat
## [1] "N"
```