Example 2. Table 2. Single-time Analysis: Two Biomakers

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Contents

1 Background

Consider a more general case in a hypothetical example shown in Figure 4 for testing two subgroups (H_1: PFS in PD-L1^+ subset (S_1); H_2: PFS in TMB high subset (S_2)) and H_3 : PFS in overall population (O) regardless of PD-L1 and TMB status. Subjects are randomized with PD-L1 status and TMB status as stratification factors. Stratified logrank tests are performed by PD-L1 status and TMB status. The numbers of events for PD-L1^+ (S_1), TMB high (S_2), $S_1 \cap S_2$, and overall population are 220, 200, 120, and 500 respectively. According to Theorem 1, the correlations among the pairwise tests are 0.57 for H_1 and H_2, 0.66 for H_1 and H_3, and 0.63 for H_2 and H_3.

```
library(corrTests)
```

2 Correlation Matrix

The correlation matrix can be obtained below.

```
corr = matrix(1, nrow=3, ncol=3)
corr[1, 2] = corr[2, 1] = corrZ(e.strat = list(AandB1=120, AnotB1=100, AandB2=120, BnotA2=80),
   e.unstr = list(A1=220, B2=200, minAorB=300),
   r.strat = list(AandB = 1/2, AnotB=1/2, BnotA=1/2),
   r.unstr = list(A=1/2, B=1/2, AandB=1/2), pAandB.unstr = 0.5,
   strat = c("Y"), method = c("Observed"))
```

```r
corr[1, 3] = corr[3, 1] = corrZ(e.strat = list(AandB1=220, AnotB1=0, AandB2=220, BnotA2=280),
   e.unstr = list(A1=220, B2=500, minAorB=500),
   r.strat = list(AandB = 1/2, AnotB=1/2, BnotA=1/2),
   r.unstr = list(A=1/2, B=1/2, AandB=1/2), pAandB.unstr = 0.5,
   strat = c("Y"), method = c("Observed"))
corr[2, 3] = corr[3, 2] = corrZ(e.strat = list(AandB1=200, AnotB1=0, AandB2=200, BnotA2=300),
   e.unstr = list(A1=200, B2=500, minAorB=500),
   r.strat = list(AandB = 1/2, AnotB=1/2, BnotA=1/2),
   r.unstr = list(A=1/2, B=1/2, AandB=1/2), pAandB.unstr = 0.5,
   strat = c("Y"), method = c("Observed"))

corr
```

```
##           [,1]      [,2]      [,3]
## [1,] 1.0000000 0.5720776 0.6633250
## [2,] 0.5720776 1.0000000 0.6324555
## [3,] 0.6633250 0.6324555 1.0000000
```

3 Different strategies of efficiency allocation

3.1 First level in the closed testing procedure: H_{123}

3.1.1 Strategy 1: Balanced: $\epsilon_{j\in J}(J) = \epsilon_J$

```r
corrBoundsST(alpha = 0.025, w = c(1/4, 1/4, 1/2), eps = c(NA,NA,NA), corr=corr)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.007548453 2.430046 1.207752 1.854707
## 2 0.00625 2.497705 0.007548453 2.430046 1.207752 1.835182
## 3 0.01250 2.241403 0.015096906 2.167539 1.207752 1.381420
```

3.1.2 Strategy 2: Maximize H_1: $\epsilon_{j\in\{J\setminus\{1\}\}}(J) = 1$

```r
corrBoundsST(alpha = 0.025, w = c(1/4, 1/4, 1/2), eps = c(NA,1,1), corr=corr)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.01159202 2.270388 1.854723 1.854708
## 2 0.00625 2.497705 0.00625000 2.497705 1.000000 1.835182
## 3 0.01250 2.241403 0.01250000 2.241403 1.000000 1.381421
```

3.1.3 Strategy 3: Maximize H_2: $\epsilon_{j\in\{J\setminus\{2\}\}}(J) = 1$

```r
corrBoundsST(alpha = 0.025, w = c(1/4, 1/4, 1/2), eps = c(1,NA,1), corr=corr)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.00625000 2.497705 1.000000 1.854696
## 2 0.00625 2.497705 0.01146999 2.274433 1.835199 1.835178
## 3 0.01250 2.241403 0.01250000 2.241403 1.000000 1.381413
```

3.1.4 Strategy 4: Maximize H_3: $\epsilon_{j\in\{J\setminus\{3\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 1/4, 1/2), eps = c(1,1,NA), corr=corr)
```

```
##        p0       z0         p        z      eps  max.eps
## 1 0.00625 2.497705 0.0062500 2.497705 1.000000 1.854714
## 2 0.00625 2.497705 0.0062500 2.497705 1.000000 1.835195
## 3 0.01250 2.241403 0.0172677 2.113764 1.381416 1.381435
```

3.1.5 Strategy 5:Maximize H_1 and H_2: $\epsilon_3(J) = 1$ and $\epsilon_1(J) = \epsilon_2(J)$.

```
corrBoundsST(alpha = 0.025, w = c(1/4, 1/4, 1/2), eps = c(NA,NA,1), corr=corr)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.008970706 2.366825 1.435313 1.854694
## 2 0.00625 2.497705 0.008970706 2.366825 1.435313 1.835188
## 3 0.01250 2.241403 0.012500000 2.241403 1.000000 1.381442
```

3.2 Second level in the closed testing procedure: H_{12}

3.2.1 $Strategy 1: Balanced: $\epsilon_{j\in J}(J) = \epsilon_J$

```
corrBoundsST(alpha = 0.025, w = c(1/2, 1/2), eps = c(NA,NA), corr=corr[1:2,1:2])
```

```
##       p0       z0          p        z      eps  max.eps
## 1 0.0125 2.241403 0.01380015 2.202921 1.104012 1.206317
## 2 0.0125 2.241403 0.01380015 2.202921 1.104012 1.206317
```

3.2.2 Strategy 2: Maximize H_1: $\epsilon_{j\in\{J\setminus\{1\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/2, 1/2), eps = c(NA,1), corr=corr[1:2,1:2])
```

```
##       p0       z0          p        z      eps  max.eps
## 1 0.0125 2.241403 0.01507896 2.168010 1.206317 1.206317
## 2 0.0125 2.241403 0.01250000 2.241403 1.000000 1.206317
```

3.2.3 Strategy 3: Maximize H_2: $\epsilon_{j\in\{J\setminus\{2\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/2, 1/2), eps = c(1,NA), corr=corr[1:2,1:2])
```

```
##       p0       z0          p        z      eps  max.eps
## 1 0.0125 2.241403 0.01250000 2.241403 1.000000 1.206317
## 2 0.0125 2.241403 0.01507896 2.168010 1.206317 1.206317
```

3.2.4 Strategy 4: Maximize H_3: $\epsilon_{j\in\{J\setminus\{3\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/2, 1/2), eps = c(NA,NA), corr=corr[1:2,1:2])
```

```
##       p0       z0          p        z      eps  max.eps
## 1 0.0125 2.241403 0.01380015 2.202921 1.104012 1.206317
## 2 0.0125 2.241403 0.01380015 2.202921 1.104012 1.206317
```

3.2.5 Strategy 5:Maximize H_1 and H_2: $\epsilon_3(J) = 1$ and $\epsilon_1(J) = \epsilon_2(J)$.

```
corrBoundsST(alpha = 0.025, w = c(1/2, 1/2), eps = c(NA,NA), corr=corr[1:2,1:2])
```

```
##       p0       z0          p        z      eps  max.eps
## 1 0.0125 2.241403 0.01380015 2.202921 1.104012 1.206317
## 2 0.0125 2.241403 0.01380015 2.202921 1.104012 1.206317
```

3.3 Second level in the closed testing procedure: H_{23}

3.3.1 $Strategy 1: Balanced: $\epsilon_{j\in J}(J) = \epsilon_J$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,NA), corr=corr[2:3,2:3])
```

```
##        p0       z0           p        z      eps  max.eps
## 1 0.00625 2.497705 0.006873855 2.463789 1.099817 1.465639
## 2 0.01875 2.080278 0.020621564 2.041077 1.099817 1.125596
```

3.3.2 Strategy 2: Maximize H_1: $\epsilon_{j\in\{J\setminus\{1\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,NA), corr=corr[2:3,2:3])
```

```
##        p0       z0           p        z      eps  max.eps
## 1 0.00625 2.497705 0.006873855 2.463789 1.099817 1.465639
## 2 0.01875 2.080278 0.020621564 2.041077 1.099817 1.125596
```

3.3.3 Strategy 3: Maximize H_2: $\epsilon_{j\in\{J\setminus\{2\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,1), corr=corr[2:3,2:3])
```

```
##        p0       z0           p        z      eps  max.eps
## 1 0.00625 2.497705 0.009160241 2.359076 1.465639 1.465639
## 2 0.01875 2.080278 0.018750000 2.080278 1.000000 1.125596
```

3.3.4 Strategy 4: Maximize H_3: $\epsilon_{j\in\{J\setminus\{3\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(1,NA), corr=corr[2:3,2:3])
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.00625000 2.497705 1.000000 1.465639
## 2 0.01875 2.080278 0.02110492 2.031445 1.125596 1.125596
```

3.3.5 Strategy 5:Maximize H_1 and H_2: $\epsilon_3(J) = 1$ and $\epsilon_1(J) = \epsilon_2(J)$.

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,1), corr=corr[2:3,2:3])
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.009160241 2.359076 1.465639 1.465639
## 2 0.01875 2.080278 0.018750000 2.080278 1.000000 1.125596
```

3.4 Second level in the closed testing procedure: H_{13}

3.4.1 $Strategy 1: Balanced: $\epsilon_{j\in J}(J) = \epsilon_J$

```
corr13 = diag(2)
corr13[1,2]=corr13[2,1]=corr[1,3]

corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,NA), corr=corr13)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.006948593 2.459910 1.111775 1.530562
## 2 0.01875 2.080278 0.020845780 2.036586 1.111775 1.139585
```

3.4.2 Strategy 2: Maximize H_1: $\epsilon_{j\in\{J\setminus\{1\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,1), corr=corr13)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.00956601 2.342949 1.530562 1.530562
## 2 0.01875 2.080278 0.01875000 2.080278 1.000000 1.139585
```

3.4.3 Strategy 3: Maximize H_2: $\epsilon_{j\in\{J\setminus\{2\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,NA), corr=corr13)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.006948593 2.459910 1.111775 1.530562
## 2 0.01875 2.080278 0.020845780 2.036586 1.111775 1.139585
```

3.4.4 Strategy 4: Maximize H_3: $\epsilon_{j\in\{J\setminus\{3\}\}}(J) = 1$

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(1,NA), corr=corr13)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.00625000 2.497705 1.000000 1.530562
## 2 0.01875 2.080278 0.02136723 2.026296 1.139585 1.139585
```

3.4.5 Strategy 5:Maximize H_1 and H_2: $\epsilon_3(J) = 1$ and $\epsilon_1(J) = \epsilon_2(J)$.

```
corrBoundsST(alpha = 0.025, w = c(1/4, 3/4), eps = c(NA,1), corr=corr13)
```

```
##        p0       z0          p        z      eps  max.eps
## 1 0.00625 2.497705 0.00956601 2.342949 1.530562 1.530562
## 2 0.01875 2.080278 0.01875000 2.080278 1.000000 1.139585
```