Results simulation study DelayedGSD

February 21, 2023

1 Rejection rate

| Power by method (columns) and scenario (rows): (nominal level | | | | | | | | | | | |
|---|-------|---------|---------|-------|----|----------|----------|----------|--|--|--|
| scenario | N | missing | binding | fixC | ar | method 1 | method 2 | method 3 | | | |
| 1 | 10000 | TRUE | TRUE | FALSE | 10 | 81.00 | 80.79 | 80.45 | | | |
| 3 | 10000 | TRUE | TRUE | FALSE | 5 | 80.60 | 80.45 | 80.21 | | | |
| 5 | 10000 | TRUE | TRUE | TRUE | 10 | 79.81 | 80.41 | 80.39 | | | |
| 7 | 10000 | TRUE | TRUE | TRUE | 5 | 80.00 | 80.46 | 80.08 | | | |
| 9 | 10000 | TRUE | FALSE | TRUE | 10 | 80.50 | 80.85 | 80.91 | | | |
| 11 | 10000 | TRUE | FALSE | TRUE | 5 | 80.73 | 80.82 | 80.75 | | | |
| 13 | 10000 | TRUE | FALSE | FALSE | 10 | 80.67 | 80.60 | 80.65 | | | |
| 15 | 10000 | TRUE | FALSE | FALSE | 5 | 80.65 | 80.64 | 80.46 | | | |
| 17 | 10000 | FALSE | TRUE | FALSE | 5 | 80.31 | 80.28 | 79.93 | | | |

⚠ slightly too high power for some scenario

Type 1 error by method (columns) and scenario (rows): (nominal level 0.025)

```
N missing binding fixC ar method 1 method 2 method 3
scenario
       2 10000
                  TRUE
                           TRUE FALSE 10
                                              2.46
                                                       2.53
                                                                 2.40
       4 10000
                  TRUE
                           TRUE FALSE 5
                                              2.42
                                                       2.41
                                                                 2.40
       6 10000
                  TRUE
                           TRUE
                                 TRUE 10
                                              2.25
                                                       2.25
                                                                 2.45
       8 10000
                  TRUE
                           TRUE
                                 TRUE 5
                                              2.42
                                                       2.39
                                                                 2.50
      10 10000
                  TRUE
                          FALSE
                                 TRUE 10
                                              2.16
                                                       2.18
                                                                 2.31
      12 10000
                  TRUE
                          FALSE
                                 TRUE 5
                                              2.36
                                                       2.35
                                                                 2.38
      14 10000
                  TRUE
                          FALSE FALSE 10
                                              2.44
                                                       2.44
                                                                 2.58
      16 10000
                  TRUE
                          FALSE FALSE 5
                                              2.51
                                                       2.50
                                                                 2.58
      18 10000
                 FALSE
                           TRUE FALSE 5
                                              2.46
                                                       2.44
                                                                 2.45
```

Type 1 error slightly below nominal level when fixC is TRUE (as expected?)

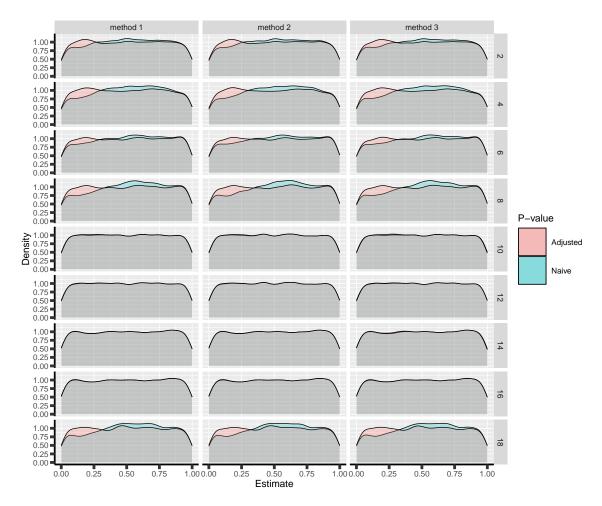


Figure 1: Naive and adjusted p-value distribution over all simulations under the null. Each row correspond to a different scenario

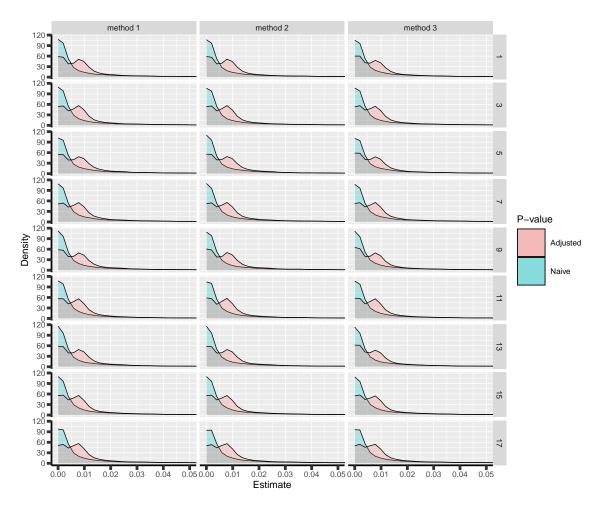


Figure 2: Naive and adjusted p-value distribution over all simulations under the alternative. Each row correspond to a different scenario

2 Conclusion of the trial

Relative frequency of stopping for efficacy/futility at decision/final

• Method 1

| | N | ${\tt missing}$ | hypo | ${\tt binding}$ | fixC | ar | decision.eff | decision.fut | final.eff | final.fut |
|-----|-------|-----------------|-------|-----------------|-------|----|--------------|--------------|-----------|-----------|
| 1: | 10000 | TRUE | power | TRUE | FALSE | 10 | 37.82 | 6.05 | 43.18 | 13.0 |
| 2: | 10000 | TRUE | typeI | TRUE | FALSE | 10 | 0.79 | 70.85 | 1.67 | 26.7 |
| 3: | 10000 | TRUE | power | TRUE | FALSE | 5 | 35.60 | 6.02 | 45.00 | 13.4 |
| 4: | 10000 | TRUE | typeI | TRUE | FALSE | 5 | 0.68 | 69.21 | 1.74 | 28.4 |
| 5: | 10000 | TRUE | power | TRUE | TRUE | 10 | 36.45 | 6.53 | 43.36 | 13.7 |
| 6: | 10000 | TRUE | typeI | TRUE | TRUE | 10 | 0.64 | 71.29 | 1.61 | 26.5 |
| 7: | 10000 | TRUE | power | TRUE | TRUE | 5 | 34.68 | 5.86 | 45.32 | 14.1 |
| 8: | 10000 | TRUE | typeI | TRUE | TRUE | 5 | 0.72 | 69.11 | 1.70 | 28.5 |
| 9: | 10000 | TRUE | power | FALSE | TRUE | 10 | 37.57 | 6.63 | 42.93 | 12.9 |
| 10: | 10000 | TRUE | typeI | FALSE | TRUE | 10 | 0.57 | 0.28 | 1.59 | 97.6 |
| 11: | 10000 | TRUE | power | FALSE | TRUE | 5 | 36.02 | 6.28 | 44.71 | 13.0 |
| 12: | 10000 | TRUE | typeI | FALSE | TRUE | 5 | 0.73 | 0.09 | 1.63 | 97.5 |
| 13: | 10000 | TRUE | power | FALSE | FALSE | 10 | 38.32 | 5.87 | 42.35 | 13.5 |
| 14: | 10000 | TRUE | typeI | FALSE | FALSE | 10 | 0.69 | 0.09 | 1.75 | 97.5 |
| 15: | 10000 | TRUE | power | FALSE | FALSE | 5 | 36.75 | 5.70 | 43.90 | 13.6 |
| 16: | 10000 | TRUE | typeI | FALSE | FALSE | 5 | 0.67 | 0.00 | 1.84 | 97.5 |
| 17: | 10000 | FALSE | power | TRUE | FALSE | 5 | 33.98 | 5.33 | 46.33 | 14.4 |
| 18: | 10000 | FALSE | typeI | TRUE | FALSE | 5 | 0.74 | 67.48 | 1.72 | 30.1 |

Method 2:

| | N | missing | hypo | binding | fixC | ar | decision.eff | decision.fut | final.eff | final.fut |
|-----|-------|---------|-------|---------|-------|----|--------------|--------------|-----------|-----------|
| 1: | 10000 | TRUE | power | TRUE | FALSE | 10 | 37.66 | 6.22 | 43.13 | 13.0 |
| 2: | 10000 | TRUE | typeI | TRUE | FALSE | 10 | 0.85 | 71.18 | 1.68 | 26.3 |
| 3: | 10000 | TRUE | power | TRUE | FALSE | 5 | 35.55 | 6.10 | 44.90 | 13.5 |
| 4: | 10000 | TRUE | typeI | TRUE | FALSE | 5 | 0.67 | 69.05 | 1.74 | 28.5 |
| 5: | 10000 | TRUE | power | TRUE | TRUE | 10 | 36.82 | 5.94 | 43.59 | 13.6 |
| 6: | 10000 | TRUE | typeI | TRUE | TRUE | 10 | 0.63 | 70.02 | 1.62 | 27.7 |
| 7: | 10000 | TRUE | power | TRUE | TRUE | 5 | 35.06 | 5.63 | 45.40 | 13.9 |
| 8: | 10000 | TRUE | typeI | TRUE | TRUE | 5 | 0.71 | 68.46 | 1.68 | 29.1 |
| 9: | 10000 | TRUE | power | FALSE | TRUE | 10 | 37.76 | 6.21 | 43.09 | 12.9 |
| 10: | 10000 | TRUE | typeI | FALSE | TRUE | 10 | 0.56 | 0.26 | 1.62 | 97.6 |
| 11: | 10000 | TRUE | power | FALSE | TRUE | 5 | 36.07 | 6.10 | 44.75 | 13.1 |
| 12: | 10000 | TRUE | typeI | FALSE | TRUE | 5 | 0.72 | 0.07 | 1.63 | 97.6 |
| 13: | 10000 | TRUE | power | FALSE | FALSE | 10 | 38.33 | 6.11 | 42.27 | 13.3 |
| 14: | 10000 | TRUE | typeI | FALSE | FALSE | 10 | 0.69 | 0.09 | 1.75 | 97.5 |
| 15: | 10000 | TRUE | power | FALSE | FALSE | 5 | 36.78 | 5.72 | 43.86 | 13.6 |
| 16: | 10000 | TRUE | typeI | FALSE | FALSE | 5 | 0.66 | 0.01 | 1.84 | 97.5 |
| 17: | 10000 | FALSE | power | TRUE | FALSE | 5 | 33.68 | 5.17 | 46.60 | 14.5 |
| 18: | 10000 | FALSE | typeI | TRUE | FALSE | 5 | 0.72 | 67.42 | 1.72 | 30.1 |

Method 3:

| | N | missing | hypo | binding | fixC | ar | decision.eff | decision.fut | final.eff | final.fut |
|-----|-------|---------|-------|---------|-------|----|--------------|--------------|-----------|-----------|
| 1: | 10000 | TRUE | power | TRUE | FALSE | 10 | 40.44 | 6.54 | 40.01 | 13.0 |
| 2: | 10000 | TRUE | typeI | TRUE | FALSE | 10 | 0.74 | 68.77 | 1.66 | 28.8 |
| 3: | 10000 | TRUE | power | TRUE | FALSE | 5 | 36.49 | 6.42 | 43.72 | 13.4 |
| 4: | 10000 | TRUE | typeI | TRUE | FALSE | 5 | 0.68 | 68.37 | 1.72 | 29.2 |
| 5: | 10000 | TRUE | power | TRUE | TRUE | 10 | 39.85 | 5.83 | 40.54 | 13.8 |
| 6: | 10000 | TRUE | typeI | TRUE | TRUE | 10 | 0.73 | 68.89 | 1.72 | 28.7 |
| 7: | 10000 | TRUE | power | TRUE | TRUE | 5 | 35.70 | 5.81 | 44.38 | 14.1 |
| 8: | 10000 | TRUE | typeI | TRUE | TRUE | 5 | 0.78 | 68.26 | 1.72 | 29.2 |
| 9: | 10000 | TRUE | power | FALSE | TRUE | 10 | 41.03 | 6.39 | 39.88 | 12.7 |
| 10: | 10000 | TRUE | typeI | FALSE | TRUE | 10 | 0.72 | 0.38 | 1.59 | 97.3 |
| 11: | 10000 | TRUE | power | FALSE | TRUE | 5 | 37.08 | 6.14 | 43.67 | 13.1 |
| 12: | 10000 | TRUE | typeI | FALSE | TRUE | 5 | 0.74 | 0.14 | 1.64 | 97.5 |
| 13: | 10000 | TRUE | power | FALSE | FALSE | 10 | 41.47 | 6.05 | 39.18 | 13.3 |
| 14: | 10000 | TRUE | typeI | FALSE | FALSE | 10 | 0.81 | 0.31 | 1.77 | 97.1 |
| 15: | 10000 | TRUE | power | FALSE | FALSE | 5 | 37.37 | 5.86 | 43.09 | 13.7 |
| 16: | 10000 | TRUE | typeI | FALSE | FALSE | 5 | 0.75 | 0.08 | 1.83 | 97.3 |
| 17: | 10000 | FALSE | power | TRUE | FALSE | 5 | 34.66 | 5.58 | 45.27 | 14.5 |
| 18: | 10000 | FALSE | typeI | TRUE | FALSE | 5 | 0.68 | 66.54 | 1.77 | 31.0 |

3 Bias (True effect: 0.6 under the alternative)

Bias per estimator and method¹:

```
biasMLE1
     hypo missing binding fixC ar
                                               biasMLE2
                                                          biasMLE3
                                                                    biasMUE1
                                                                              biasMUE2 biasMUE3
 1: power
             TRUE
                     TRUE FALSE 10
                                     0.012970
                                               0.013058
                                                          0.014139
                                                                    0.005472
                                                                              0.005564
                                                                                         0.00216
 2: typeI
             TRUE
                     TRUE FALSE 10 -0.018416 -0.018430 -0.018509 -0.004261 -0.004326 -0.00464
 3: power
             TRUE
                     TRUE FALSE
                                 5
                                    0.022430
                                               0.022231
                                                          0.023386
                                                                   0.010079
                                                                              0.010156
                                                                                         0.00864
 4: typeI
                     TRUE FALSE
                                  5 -0.030419 -0.030822 -0.030577 -0.011757 -0.012140 -0.01213
             TRUE
                                    0.011558 0.012119
                                                          0.012968
                                                                   0.001017
                                                                             0.001972 0.00212
 5: power
             TRUE
                     TRUE
                           TRUE 10
 6: typeI
             TRUE
                     TRUE
                           TRUE 10 -0.022074 -0.022256 -0.022266 -0.008120 -0.008149 -0.00830
7: power
             TRUE
                     TRUE
                           TRUE
                                    0.021638 0.022029
                                                          0.022692 0.008407
                                                                             0.008660
                                                                                         0.00842
                           TRUE
                                  5 -0.033857 -0.034379 -0.034138 -0.014560 -0.014719 -0.01503
 8: typeI
             TRUE
                     TRUE
 9: power
             TRUE
                    FALSE
                           TRUE 10
                                     0.015026
                                               0.015050
                                                          0.016312
                                                                    0.000405
                                                                              0.000655
                                                                                         0.00121
10: typeI
             TRUE
                    FALSE
                           TRUE 10
                                     0.000543
                                               0.000547
                                                          0.000883
                                                                    0.001271
                                                                              0.001309
                                                                                         0.00208
11: power
             TRUE
                    FALSE
                           TRUE
                                     0.024204
                                               0.024192
                                                                    0.006976
                                 5
                                                          0.025190
                                                                              0.006478
                                                                                         0.00759
                           TRUE
12: typeI
             TRUE
                    FALSE
                                 5
                                     0.001472
                                               0.001451
                                                          0.001545
                                                                    0.001680
                                                                              0.001708
                                                                                         0.00172
             TRUE
                    FALSE FALSE 10
                                     0.014415
                                                                    0.003384
13: power
                                               0.014146
                                                          0.015747
                                                                              0.002971
                                                                                         0.00239
                    FALSE FALSE 10
14: typeI
             TRUE
                                     0.000139
                                               0.000139
                                                          0.000555
                                                                    0.000611
                                                                              0.000628
                                                                                         0.00181
                    FALSE FALSE
                                     0.023380
                                                                    0.008843
15: power
             TRUE
                                  5
                                               0.023344
                                                          0.024346
                                                                              0.008827
                                                                                         0.00767
16: typeI
                                  5
                                     0.000602
                                               0.000602
             TRUE
                    FALSE FALSE
                                                          0.000949
                                                                    0.000637
                                                                               0.000599
                                                                                         0.00125
                                  5
                                     0.022836
                                               0.022825
                                                          0.023807
17: power
            FALSE
                     TRUE FALSE
                                                                    0.011971
                                                                              0.012078
                                                                                         0.01031
18: typeI
            FALSE
                     TRUE FALSE
                                  5 -0.029516 -0.029722 -0.029915 -0.011048 -0.011395 -0.01144
```

Median bias ² per estimator and method:

| | | 1 | | | | | | | | |
|-------|---|---|--|---|---|--|--|--|---|---|
| hypo | missing | ${\tt binding}$ | fixC | ar | ${\tt mbiasMLE1}$ | ${\tt mbiasMLE2}$ | ${\tt mbiasMLE3}$ | ${\tt mbias MUE1}$ | ${\tt mbias MUE2}$ | mbiasMUE3 |
| power | TRUE | TRUE | FALSE | 10 | 0.0250 | 0.0240 | 0.0266 | -0.0023 | -0.0017 | -0.0062 |
| typeI | TRUE | TRUE | FALSE | 10 | -0.0193 | -0.0198 | -0.0223 | 0.0002 | -0.0013 | 0.0001 |
| power | TRUE | TRUE | FALSE | 5 | 0.0387 | 0.0382 | 0.0406 | -0.0030 | -0.0016 | -0.0026 |
| typeI | TRUE | TRUE | FALSE | 5 | -0.0346 | -0.0339 | -0.0361 | 0.0000 | -0.0002 | 0.0001 |
| power | TRUE | TRUE | TRUE | 10 | 0.0164 | 0.0188 | 0.0179 | -0.0132 | -0.0126 | -0.0101 |
| typeI | TRUE | TRUE | TRUE | 10 | -0.0327 | -0.0314 | -0.0347 | -0.0113 | -0.0079 | -0.0099 |
| power | TRUE | TRUE | TRUE | 5 | 0.0356 | 0.0369 | 0.0361 | -0.0106 | -0.0114 | -0.0082 |
| typeI | TRUE | TRUE | TRUE | 5 | -0.0473 | -0.0492 | -0.0493 | -0.0105 | -0.0081 | -0.0105 |
| power | TRUE | FALSE | TRUE | 10 | 0.0328 | 0.0301 | 0.0345 | -0.0089 | -0.0106 | -0.0055 |
| typeI | TRUE | FALSE | TRUE | 10 | 0.0007 | -0.0019 | 0.0007 | 0.0024 | -0.0005 | 0.0034 |
| power | TRUE | FALSE | TRUE | 5 | 0.0479 | 0.0459 | 0.0499 | -0.0049 | -0.0048 | -0.0034 |
| typeI | TRUE | FALSE | TRUE | 5 | 0.0009 | -0.0017 | 0.0009 | 0.0012 | -0.0012 | 0.0020 |
| power | TRUE | FALSE | FALSE | 10 | 0.0326 | 0.0324 | 0.0339 | -0.0033 | -0.0036 | -0.0004 |
| typeI | TRUE | FALSE | FALSE | 10 | -0.0039 | -0.0039 | -0.0037 | -0.0031 | -0.0030 | -0.0011 |
| power | TRUE | FALSE | FALSE | 5 | 0.0442 | 0.0442 | 0.0465 | -0.0010 | -0.0010 | -0.0037 |
| typeI | TRUE | FALSE | FALSE | 5 | -0.0039 | -0.0039 | -0.0039 | -0.0039 | -0.0039 | -0.0028 |
| power | FALSE | TRUE | FALSE | 5 | 0.0383 | 0.0378 | 0.0400 | -0.0026 | -0.0008 | -0.0046 |
| typeI | FALSE | TRUE | FALSE | 5 | -0.0329 | -0.0336 | -0.0353 | 0.0044 | 0.0031 | 0.0035 |
| | power typeI power | power TRUE typeI TRUE TRUE power TRUE typeI TRUE power TRUE | power TRUE TRUE typeI TRUE TRUE power TRUE TRUE typeI TRUE TRUE power TRUE TRUE typeI TRUE TRUE typeI TRUE TRUE power TRUE TRUE typeI TRUE TRUE typeI TRUE FALSE power TRUE FALSE typeI TRUE FALSE power TRUE FALSE | power TRUE TRUE FALSE typeI TRUE TRUE FALSE power TRUE TRUE FALSE typeI TRUE TRUE FALSE typeI TRUE TRUE TRUE FALSE power TRUE TRUE TRUE typeI TRUE TRUE TRUE power TRUE TRUE TRUE typeI TRUE TRUE TRUE typeI TRUE FALSE TRUE typeI TRUE FALSE TRUE typeI TRUE FALSE TRUE typeI TRUE FALSE TRUE power TRUE FALSE TRUE typeI TRUE FALSE TRUE typeI TRUE FALSE FALSE typeI TRUE FALSE FALSE typeI TRUE FALSE FALSE typeI TRUE FALSE FALSE power TRUE FALSE FALSE typeI TRUE FALSE FALSE typeI TRUE FALSE FALSE | power TRUE TRUE FALSE 10 typeI TRUE TRUE FALSE 10 power TRUE TRUE FALSE 5 typeI TRUE TRUE FALSE 5 power TRUE TRUE TRUE 10 typeI TRUE TRUE TRUE 10 power TRUE TRUE TRUE 5 typeI TRUE TRUE TRUE 5 typeI TRUE TRUE TRUE 5 power TRUE FALSE TRUE 10 typeI TRUE FALSE TRUE 10 power TRUE FALSE TRUE 5 typeI TRUE FALSE TRUE 5 typeI TRUE FALSE TRUE 5 typeI TRUE FALSE FALSE 10 power TRUE FALSE FALSE 10 power TRUE FALSE FALSE 5 typeI TRUE FALSE FALSE 5 typeI TRUE FALSE FALSE 5 | power TRUE TRUE FALSE 10 0.0250 typeI TRUE TRUE FALSE 10 -0.0193 power TRUE TRUE FALSE 5 0.0387 typeI TRUE TRUE FALSE 5 -0.0346 power TRUE TRUE TRUE 10 0.0164 typeI TRUE TRUE TRUE 10 -0.0327 power TRUE TRUE TRUE 5 -0.0473 power TRUE FALSE TRUE 10 0.0328 typeI TRUE FALSE TRUE 10 0.0027 power TRUE FALSE TRUE 5 0.0479 typeI TRUE FALSE TRUE 5 0.0009 power TRUE FALSE FALSE 10 -0.0039 power TRUE FALSE 5 0.0442 typeI TRUE FALSE | power TRUE TRUE FALSE 10 0.0250 0.0240 typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 power TRUE TRUE FALSE 5 0.0387 0.0382 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 power TRUE TRUE TRUE 10 0.0164 0.0188 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 power TRUE TRUE TRUE 5 0.0356 0.0369 typeI TRUE TRUE TRUE 5 -0.0473 -0.0492 power TRUE FALSE TRUE 10 0.0328 0.0301 typeI TRUE FALSE TRUE 5 0.0479 0.0459 typeI TRUE FALSE TRUE 5 0.0009 -0.0017 power TRUE FALSE FALSE <td>power TRUE TRUE FALSE 10 0.0250 0.0240 0.0266 typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 -0.0223 power TRUE TRUE FALSE 5 0.0387 0.0382 0.0406 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 -0.0361 power TRUE TRUE TRUE 10 0.0164 0.0188 0.0179 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 -0.0347 power TRUE TRUE TRUE 5 0.0356 0.0369 0.0361 typeI TRUE TRUE 5 -0.0473 -0.0492 -0.0493 power TRUE FALSE TRUE 10 0.0328 0.0301 0.0345 typeI TRUE FALSE TRUE 5 0.0479 0.0459 0.0499 typeI TRUE</td> <td>power TRUE TRUE FALSE 10 0.0250 0.0240 0.0266 -0.0023 typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 -0.0223 0.0002 power TRUE TRUE FALSE 5 0.0387 0.0382 0.0406 -0.0030 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 -0.0361 0.0000 power TRUE TRUE TRUE 10 0.0164 0.0188 0.0179 -0.0132 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 -0.0347 -0.0113 power TRUE TRUE TRUE 5 0.0356 0.0369 0.0361 -0.0106 typeI TRUE FALSE TRUE 10 0.0328 0.0301 0.0345 -0.0089 typeI TRUE FALSE TRUE 5 0.0479 0.0459 0.0499 -0.0049</td> <td>typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 -0.0223 0.0002 -0.0013 power TRUE TRUE FALSE 5 0.0387 0.0382 0.0406 -0.0030 -0.0016 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 -0.0361 0.0000 -0.0002 power TRUE TRUE TRUE 10 0.0164 0.0188 0.0179 -0.0132 -0.0126 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 -0.0347 -0.0113 -0.0079 power TRUE TRUE TRUE 5 0.0356 0.0369 0.0361 -0.0106 -0.0114 typeI TRUE TRUE TRUE 5 -0.0473 -0.0492 -0.0493 -0.0105 -0.0081 power TRUE FALSE TRUE 10 0.0027 -0.0019 0.0007 0.0024 -0.0089 -0.0106 typeI TRUE FALSE TRUE 5 0.00479 0.0459 0.0499 -0.0049</td> | power TRUE TRUE FALSE 10 0.0250 0.0240 0.0266 typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 -0.0223 power TRUE TRUE FALSE 5 0.0387 0.0382 0.0406 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 -0.0361 power TRUE TRUE TRUE 10 0.0164 0.0188 0.0179 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 -0.0347 power TRUE TRUE TRUE 5 0.0356 0.0369 0.0361 typeI TRUE TRUE 5 -0.0473 -0.0492 -0.0493 power TRUE FALSE TRUE 10 0.0328 0.0301 0.0345 typeI TRUE FALSE TRUE 5 0.0479 0.0459 0.0499 typeI TRUE | power TRUE TRUE FALSE 10 0.0250 0.0240 0.0266 -0.0023 typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 -0.0223 0.0002 power TRUE TRUE FALSE 5 0.0387 0.0382 0.0406 -0.0030 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 -0.0361 0.0000 power TRUE TRUE TRUE 10 0.0164 0.0188 0.0179 -0.0132 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 -0.0347 -0.0113 power TRUE TRUE TRUE 5 0.0356 0.0369 0.0361 -0.0106 typeI TRUE FALSE TRUE 10 0.0328 0.0301 0.0345 -0.0089 typeI TRUE FALSE TRUE 5 0.0479 0.0459 0.0499 -0.0049 | typeI TRUE TRUE FALSE 10 -0.0193 -0.0198 -0.0223 0.0002 -0.0013 power TRUE TRUE FALSE 5 0.0387 0.0382 0.0406 -0.0030 -0.0016 typeI TRUE TRUE FALSE 5 -0.0346 -0.0339 -0.0361 0.0000 -0.0002 power TRUE TRUE TRUE 10 0.0164 0.0188 0.0179 -0.0132 -0.0126 typeI TRUE TRUE TRUE 10 -0.0327 -0.0314 -0.0347 -0.0113 -0.0079 power TRUE TRUE TRUE 5 0.0356 0.0369 0.0361 -0.0106 -0.0114 typeI TRUE TRUE TRUE 5 -0.0473 -0.0492 -0.0493 -0.0105 -0.0081 power TRUE FALSE TRUE 10 0.0027 -0.0019 0.0007 0.0024 -0.0089 -0.0106 typeI TRUE FALSE TRUE 5 0.00479 0.0459 0.0499 -0.0049 |

¹e.g. biasMLE1 mixed model estimator (treatment effect), method 1 (boundaries)

²Relative frequency at which the estimate is greater than the truth minus 0.5

4 Distribution of the estimates

Distribution of the estimates:

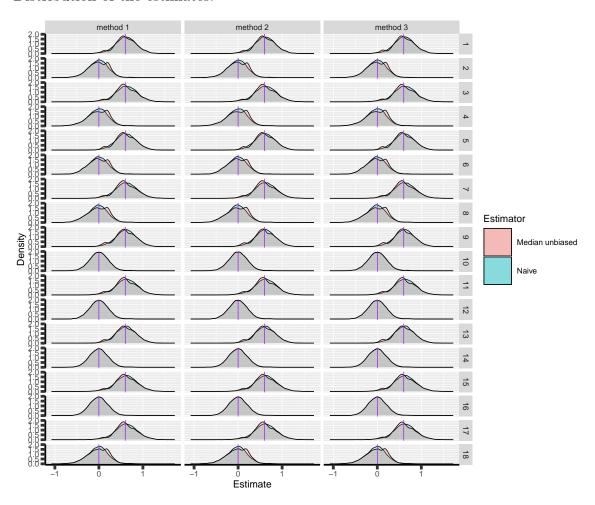


Figure 3: Naive and Median unbiased estimate distribution over all simulations. Each row correspond to a different scenario

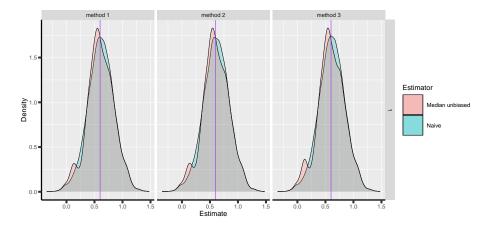


Figure 4: Same but specific to scenario 1

Distribution of the median unbiased estimate conditional to the stage:

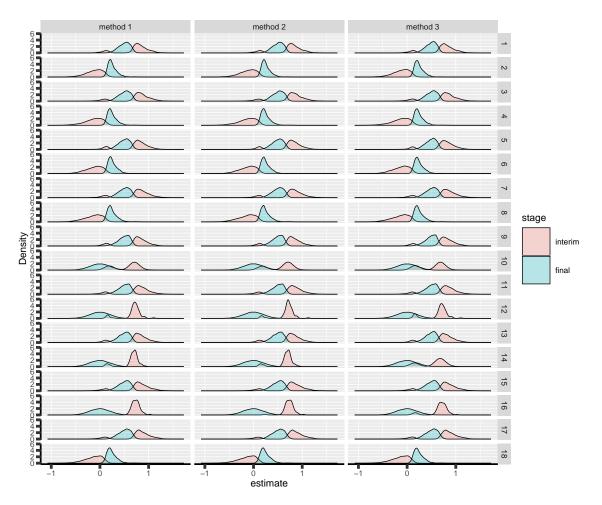


Figure 5: Median unbiased estimate distribution conditional to the stage. Each row correspond to a different scenario.

5 Special cases

Reason for stopping (first 4) or continuing the trial (last):

| | | scenario | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|----------|---|---|---|--|--|---|--|--|
| reason | method | | | | | | | | | |
| decreasing information | 1 | | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| | 2 | | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| | 3 | | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| efficacy | 1 | | 3740 | | 3559 | 67 | 3696 | 82 | 3502 | 82 |
| | 2 | | 3729 | 82 | 3554 | 68 | 3732 | 82 | 3546 | 83 |
| | 3 | | 4137 | 107 | 3712 | 83 | 4071 | 110 | 3632 | 92 |
| futility | 1 | | 646 | 7086 | 603 | 6922 | 600 | 7109 | 552 | 6901 |
| | 2 | | 658 | 7120 | 611 | 6904 | 542 | 6981 | 523 | 6834 |
| | 3 | | 560 | 6843 | 579 | 6822 | 495 | 6850 | 519 | 6812 |
| Imax reached | 1 | | 1 | 1 | 0 | 0 | 2 | 2 | 0 | 0 |
| | 2 | | 1 | 1 | 0 | 0 | 2 | 2 | 0 | 0 |
| | 3 | | 1 | 1 | 0 | 0 | 2 | 2 | 0 | 0 |
| no boundary crossed | 1 | | 5613 | 2836 | 5838 | 3011 | 5702 | 2807 | 5946 | 3017 |
| | 2 | | 5612 | 2797 | 5835 | 3028 | 5724 | 2935 | 5931 | 3083 |
| | 3 | | 5302 | 3049 | 5709 | 3095 | 5432 | 3038 | 5849 | 3096 |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | scenario | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| reason | method | scenario | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| reason decreasing information | | scenario | 9 | 10 | 11 | 12 | 13 | 14 | 15 0 | 16 0 |
| | | scenario | | | | | | | | |
| | 1 | scenario | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 1 2 | scenario | 0 | 0 0 | 1 | 0 0 | 0 | 0 0 | 0 | 0 |
| decreasing information | 1 2 3 | scenario | 0 0 | 0 0 0 84 | 1 1 1 | 0 0 0 82 | 0 0 | 0 0 0 78 | 0 0 | 0 0 |
| decreasing information | 1 2 3 1 | scenario | 0 0 0 3805 | 0 0 0 84 81 | 1 1 1 3634 | 0 0 0 82 79 | 0 0 0 3815 | 0 0 0 78 78 | 0 0 0 3674 | 0 0 0 67 |
| decreasing information | 1 2 3 1 2 | scenario | 0 0 0 3805 3824 4206 | 0 0 0 84 81 | 1 1 1 3634 3646 3761 | 0 0 0 82 79 | 0 0 0 3815 3816 4238 | 0 0 0 78 78 | 0 0 0 3674 3677 3788 | 0 0 0 67 67 |
| decreasing information efficacy | 1 2 3 1 2 3 | scenario | 0 0 0 3805 3824 4206 614 | 0 0 0 84 81 109 | 1 1 3634 3646 3761 596 | 0 0 0 82 79 88 | 0 0 0 3815 3816 4238 604 | 0 0 0 78 78 112 | 0 0 0 3674 3677 3788 571 | 0 0 0 67 67 83 |
| decreasing information efficacy | 1 2 3 1 2 3 1 | scenario | 0 0 0 3805 3824 4206 614 572 | 0 0 0 84 81 109 7130 | 1 1 3634 3646 3761 596 571 | 0 0 0 82 79 88 6957 | 0 0 0 3815 3816 4238 604 628 | 0 0 0 78 78 112 7126 | 0 0 0 3674 3677 3788 571 573 | 0 0 0 67 67 83 6920 |
| decreasing information efficacy | 1 2 3 1 2 3 1 2 | scenario | 0 0 0 3805 3824 4206 614 572 | 0 0 0 84 81 109 7130 7044 | 1 1 3634 3646 3761 596 571 | 0 0 0 82 79 88 6957 6907 | 0 0 0 3815 3816 4238 604 628 | 0 0 78 78 112 7126 7180 | 0 0 0 3674 3677 3788 571 573 | 0 0 0 67 67 83 6920 |
| decreasing information efficacy futility | 1 2 3 1 2 3 1 2 3 | scenario | 0 0 3805 3824 4206 614 572 535 | 0 0 0 84 81 109 7130 7044 6914 | 1 1 3634 3646 3761 596 571 561 | 0 0 0 82 79 88 6957 6907 6867 | 0 0 0 3815 3816 4238 604 628 514 | 0 0 78 78 112 7126 7180 6870 | 0 0 0 3674 3677 3788 571 573 535 | 0 0 0 67 67 83 6920 6925 6837 |
| decreasing information efficacy futility | 1 2 3 1 2 3 1 2 3 1 2 3 | scenario | 0 0 3805 3824 4206 614 572 535 | 0 0 84 81 109 7130 7044 6914 | 1 1 3634 3646 3761 596 571 561 | 0 0 82 79 88 6957 6907 6867 0 | 0 0 3815 3816 4238 604 628 514 0 | 0 0 78 78 112 7126 7180 6870 0 | 0 0 0 3674 3677 3788 571 573 535 0 | 0 0 67 67 83 6920 6925 6837 0 |
| decreasing information efficacy futility | 1 2 3 1 2 3 1 2 3 1 2 3 | scenario | 0 0 3805 3824 4206 614 572 535 1 1 | 0 0 84 81 109 7130 7044 6914 1 | 1 1 3634 3646 3761 596 571 561 0 0 | 0 0 82 79 88 6957 6907 6867 0 0 | 0 0 0 3815 3816 4238 604 628 514 0 0 | 0 0 78 78 112 7126 7180 6870 0 0 | 0 0 3674 3677 3788 571 573 535 0 | 0 0 67 67 83 6920 6925 6837 0 0 |
| decreasing information efficacy futility Imax reached | 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 | scenario | 0 0 3805 3824 4206 614 572 535 1 1 1 | 0 0 84 81 109 7130 7044 6914 1 1 2785 | 1 1 3634 3646 3761 596 571 561 0 0 5770 | 0 0 0 82 79 88 6957 6907 6867 0 0 | 0 0 3815 3816 4238 604 628 514 0 0 0 | 0 0 78 78 112 7126 7180 6870 0 0 2796 | 0 0 3674 3677 3788 571 573 535 0 0 | 0 0 67 67 83 6920 6925 6837 0 0 3013 |
| decreasing information efficacy futility Imax reached | 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 | scenario | 0 0 3805 3824 4206 614 572 535 1 1 5580 5603 | 0 0 84 81 109 7130 7044 6914 1 1 2785 2874 | 1 1 3634 3646 3761 596 571 561 0 0 5770 5783 | 0 0 82 79 88 6957 6907 6867 0 0 2961 3014 | 0 0 0 3815 3816 4238 604 628 514 0 0 5581 5556 | 0 0 78 78 112 7126 7180 6870 0 0 2796 2742 | 0 0 0 3674 3677 3788 571 573 535 0 0 5755 | 0 0 67 67 83 6920 6925 6837 0 0 3013 3008 |

6 Reversal probability

Percentage of time we observe a reversal:

| | N | hypo | missing | ar | binding | fixC | fu2eff_1 | fu2eff_2 | fu2eff_3 | eff2fu_1 | eff2fu_2 | eff2fu_3 |
|-----|-------|-------|---------|----|---------|-------|----------|----------|----------|----------|----------|----------|
| 1: | 10000 | power | FALSE | 5 | TRUE | FALSE | 0.06 | 0.07 | 0.01 | 0.04 | 0.04 | 0.63 |
| 2: | 10000 | power | TRUE | 5 | FALSE | FALSE | 0.04 | 0.04 | 0.00 | 0.03 | 0.03 | 0.51 |
| 3: | 10000 | power | TRUE | 5 | FALSE | TRUE | 0.04 | 0.03 | 0.03 | 0.36 | 0.42 | 0.56 |
| 4: | 10000 | power | TRUE | 5 | TRUE | FALSE | 0.06 | 0.08 | 0.02 | 0.05 | 0.07 | 0.65 |
| 5: | 10000 | power | TRUE | 5 | TRUE | TRUE | 0.02 | 0.02 | 0.01 | 0.36 | 0.42 | 0.63 |
| 6: | 10000 | power | TRUE | 10 | FALSE | FALSE | 0.35 | 0.38 | 0.05 | 0.18 | 0.21 | 0.96 |
| 7: | 10000 | power | TRUE | 10 | FALSE | TRUE | 0.15 | 0.13 | 0.10 | 0.63 | 0.61 | 1.13 |
| 8: | 10000 | power | TRUE | 10 | TRUE | FALSE | 0.57 | 0.57 | 0.13 | 0.15 | 0.20 | 1.06 |
| 9: | 10000 | power | TRUE | 10 | TRUE | TRUE | 0.17 | 0.16 | 0.11 | 0.70 | 0.68 | 0.99 |
| 10: | 10000 | typeI | FALSE | 5 | TRUE | FALSE | 0.01 | 0.03 | 0.00 | 0.01 | 0.03 | 0.12 |
| 11: | 10000 | typeI | TRUE | 5 | FALSE | FALSE | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.08 |
| 12: | 10000 | typeI | TRUE | 5 | FALSE | TRUE | 0.00 | 0.00 | 0.00 | 0.09 | 0.07 | 0.14 |
| 13: | 10000 | typeI | TRUE | 5 | TRUE | FALSE | 0.02 | 0.02 | 0.00 | 0.01 | 0.03 | 0.15 |
| 14: | 10000 | typeI | TRUE | 5 | TRUE | TRUE | 0.00 | 0.00 | 0.00 | 0.10 | 0.12 | 0.14 |
| 15: | 10000 | typeI | TRUE | 10 | FALSE | FALSE | 0.00 | 0.00 | 0.00 | 0.09 | 0.09 | 0.31 |
| 16: | 10000 | typeI | TRUE | 10 | FALSE | TRUE | 0.00 | 0.00 | 0.00 | 0.27 | 0.25 | 0.37 |
| 17: | 10000 | typeI | TRUE | 10 | TRUE | FALSE | 0.11 | 0.11 | 0.03 | 0.09 | 0.08 | 0.36 |
| 18: | 10000 | typeI | TRUE | 10 | TRUE | TRUE | 0.02 | 0.00 | 0.00 | 0.22 | 0.21 | 0.39 |

7 Frequency mismatch p-value / boundaries

When concluding for futility:

```
hypo missing ar binding fixC
                                    method 1
                                                method 2
                                                           method 3
 1: power
           FALSE 5
                       TRUE FALSE 0.00000000 0.00000000 0.74738416
2: power
            TRUE 5
                      FALSE FALSE 0.41343669 0.41322314 0.56294780
3: power
            TRUE 5
                      FALSE TRUE 1.34924754 0.93847758 0.57142857
4: power
            TRUE 5
                       TRUE FALSE 0.00000000 0.00000000 0.55583628
5: power
            TRUE 5
                       TRUE TRUE 2.55000000 1.84237462 0.65261044
 6: power
            TRUE 10
                      FALSE FALSE 2.43145370 2.47422680 1.34366925
7: power
            TRUE 10
                      FALSE TRUE 3.33333333 3.39425587 0.68098481
8: power
            TRUE 10
                       TRUE FALSE 0.00000000 0.00000000 1.07416880
9: power
            TRUE 10
                       TRUE TRUE 3.91282813 3.77743747 1.22386537
10: typeI
           FALSE 5
                       TRUE FALSE 0.00000000 0.00000000 0.02050231
                      FALSE FALSE 0.03077239 0.03076923 0.06158900
11: typeI
            TRUE 5
                       FALSE TRUE 0.07169193 0.06144393 0.02048760
12: typeI
            TRUE 5
                       TRUE FALSE 0.00000000 0.00000000 0.02049180
13: typeI
            TRUE 5
                       TRUE TRUE 0.14347202 0.12293822 0.02051282
14: typeI
            TRUE 5
15: typeI
            TRUE 10
                       FALSE FALSE 0.14350144 0.14350144 0.10264833
16: typeI
            TRUE 10
                      FALSE TRUE 0.20441537 0.16356573 0.05118231
            TRUE 10
                       TRUE FALSE 0.00000000 0.00000000 0.01024590
17: typeI
18: typeI
            TRUE 10
                       TRUE TRUE 0.26598465 0.25575448 0.09226038
```

When concluding for efficacy:

| | hypo | missing | ar | ${\tt binding}$ | fixC | ${\tt method}$ | 1 | ${\tt method}$ | 2 | ${\tt method}$ | 3 |
|-----|-------|---------|----|-----------------|-------|----------------|---|----------------|---|----------------|---|
| 1: | power | FALSE | 5 | TRUE | FALSE | | 0 | | 0 | | 0 |
| 2: | power | TRUE | 5 | FALSE | FALSE | | 0 | | 0 | | 0 |
| 3: | power | TRUE | 5 | FALSE | TRUE | | 0 | | 0 | | 0 |
| 4: | power | TRUE | 5 | TRUE | FALSE | | 0 | | 0 | | 0 |
| 5: | power | TRUE | 5 | TRUE | TRUE | | 0 | | 0 | | 0 |
| 6: | power | TRUE | 10 | FALSE | FALSE | | 0 | | 0 | | 0 |
| 7: | power | TRUE | 10 | FALSE | TRUE | | 0 | | 0 | | 0 |
| 8: | power | TRUE | 10 | TRUE | FALSE | | 0 | | 0 | | 0 |
| 9: | power | TRUE | 10 | TRUE | TRUE | | 0 | | 0 | | 0 |
| 10: | typeI | FALSE | 5 | TRUE | FALSE | | 0 | | 0 | | 0 |
| 11: | typeI | TRUE | 5 | FALSE | FALSE | | 0 | | 0 | | 0 |
| 12: | typeI | TRUE | 5 | FALSE | TRUE | | 0 | | 0 | | 0 |
| 13: | typeI | TRUE | 5 | TRUE | FALSE | | 0 | | 0 | | 0 |
| 14: | typeI | TRUE | 5 | TRUE | TRUE | | 0 | | 0 | | 0 |
| 15: | typeI | TRUE | 10 | FALSE | FALSE | | 0 | | 0 | | 0 |
| 16: | typeI | TRUE | 10 | FALSE | TRUE | | 0 | | 0 | | 0 |
| 17: | typeI | TRUE | 10 | TRUE | FALSE | | 0 | | 0 | | 0 |
| 18: | typeI | TRUE | 10 | TRUE | TRUE | | 0 | | 0 | | 0 |

8 Percentage of missing values

Here only for method 1 - values are very similar between different methods:

- pc.all percentage of observations with full data
- pc.missing3 percentage of observations missing the final outcome but with intermediate outcome value and baseline.
- pc.missing23 percentage of observations with only baseline value

| | ${\tt method}$ | missing | ar | hypo | fixC | binding | N | pc.all | <pre>pc.missing3</pre> | pc.missing23 |
|-----|----------------|---------|----|-------|-------|---------|-------|----------|------------------------|--------------|
| 1: | 1 | TRUE | 5 | power | FALSE | TRUE | 10000 | 79.53472 | 9.562374 | 10.902910 |
| 2: | 1 | TRUE | 5 | typeI | FALSE | TRUE | 10000 | 79.53472 | 9.562374 | 10.902910 |
| 3: | 1 | TRUE | 5 | power | TRUE | TRUE | 10000 | 79.44022 | 9.531225 | 11.028558 |
| 4: | 1 | TRUE | 5 | typeI | TRUE | TRUE | 10000 | 79.44022 | 9.531225 | 11.028558 |
| 5: | 1 | TRUE | 5 | power | TRUE | FALSE | 10000 | 79.71917 | 9.427430 | 10.853396 |
| 6: | 1 | TRUE | 5 | typeI | TRUE | FALSE | 10000 | 79.71917 | 9.427430 | 10.853396 |
| 7: | 1 | TRUE | 5 | power | FALSE | FALSE | 10000 | 79.64196 | 9.449136 | 10.908902 |
| 8: | 1 | TRUE | 5 | typeI | FALSE | FALSE | 10000 | 79.64196 | 9.449136 | 10.908902 |
| 9: | 1 | FALSE | 5 | power | FALSE | TRUE | 10000 | 87.78863 | 6.090240 | 6.121126 |
| 10: | 1 | FALSE | 5 | typeI | FALSE | TRUE | 10000 | 87.78863 | 6.090240 | 6.121126 |
| 11: | 1 | TRUE | 10 | power | FALSE | TRUE | 10000 | 71.60971 | 13.327969 | 15.062319 |
| 12: | 1 | TRUE | 10 | typeI | FALSE | TRUE | 10000 | 71.60971 | 13.327969 | 15.062319 |
| 13: | 1 | TRUE | 10 | power | TRUE | TRUE | 10000 | 71.52189 | 13.282615 | 15.195496 |
| 14: | 1 | TRUE | 10 | typeI | TRUE | TRUE | 10000 | 71.52189 | 13.282615 | 15.195496 |
| 15: | 1 | TRUE | 10 | power | TRUE | FALSE | 10000 | 71.85935 | 13.144488 | 14.996166 |
| 16: | 1 | TRUE | 10 | typeI | TRUE | FALSE | 10000 | 71.85935 | 13.144488 | 14.996166 |
| 17: | 1 | TRUE | 10 | power | FALSE | FALSE | 10000 | 71.79364 | 13.168843 | 15.037522 |
| 18: | 1 | TRUE | 10 | typeI | FALSE | FALSE | 10000 | 71.79364 | 13.168843 | 15.037522 |

9 Information

Percentage of information for method 1^3 :

```
scenario missing binding fixC ar interim decision
                                                        final
           TRUE
                    TRUE FALSE 10 54.63862 63.33698 102.69943
       1
      2
           TRUE
                    TRUE FALSE 10 54.63862 68.96135 102.32310
      3
                    TRUE FALSE 5 53.27109 57.38550 102.74966
           TRUE
      4
                    TRUE FALSE 5 53.27109 60.22345 102.34459
           TRUE
      5
           TRUE
                    TRUE
                         TRUE 10 54.54008 63.10923 102.78945
                          TRUE 10 54.54008 68.95137 102.12003
      6
           TRUE
                    TRUE
      7
           TRUE
                    TRUE
                          TRUE
                               5 53.17744 57.18426 102.80673
                          TRUE 5 53.17744 60.12266 102.22328
      8
           TRUE
                    TRUE
      9
           TRUE
                   FALSE
                          TRUE 10 54.51044 63.16647 102.56935
                   FALSE
                         TRUE 10 54.51044 54.66970 103.09893
      10
           TRUE
                          TRUE
                                5 53.17317 57.27740 102.61166
      11
           TRUE
                   FALSE
                                5 53.17317 53.24797 103.10060
      12
           TRUE
                   FALSE
                         TRUE
                   FALSE FALSE 10 54.49750 63.16580 102.56590
      13
           TRUE
           TRUE
                   FALSE FALSE 10 54.49750 54.64468 103.12067
     14
                   FALSE FALSE 5 53.15611 57.29003 102.60917
           TRUE
     15
                   FALSE FALSE 5 53.15611 53.21806 103.12463
      16
           TRUE
     17
           FALSE
                    TRUE FALSE 5 52.06840 56.28978 99.96969
                    TRUE FALSE 5 52.06840 59.42197 99.62860
      18
           FALSE
```

Similar results for other methods.

³average over the reached stages