Results simulation study DelayedGSD

September 8, 2023

1 Rejection rate

Power by r	nethod	l (column	s) and so	ws):	(n	nominal level 80%)		
scenario	n.sim	missing	binding	fixC	ar	method 1	method 2	method 3
1	10000	TRUE	TRUE	FALSE	10	81.00	80.93	80.43
3	10000	TRUE	TRUE	FALSE	5	80.53	80.53	80.14
5	10000	TRUE	TRUE	TRUE	10	80.15	80.35	80.43
7	10000	TRUE	TRUE	TRUE	5	80.08	80.20	80.14
9	10000	TRUE	FALSE	TRUE	10	79.86	80.12	80.26
11	10000	TRUE	FALSE	TRUE	5	79.93	80.04	80.06
13	10000	TRUE	FALSE	FALSE	10	80.50	80.44	80.26
15	10000	TRUE	FALSE	FALSE	5	80.37	80.36	80.06
17	10000	FALSE	TRUE	FALSE	5	80.31	80.30	79.92
Type 1	error l	oy metho	d (colum	ns) and	d sc	cenario (ro	ws): (ne	ominal level 2.5%)
scenario	n.sim	missing	binding	fixC	ar	method 1	method 2	method 3
2	10000	TRUE	TRUE	FALSE	10	2.42	2.39	2.37
4	10000	TRUE	TRUE	FALSE	5	2.40	2.40	2.35
6	10000	TRUE	TRUE	TRUE	10	2.24	2.22	2.37
8	10000	TRUE	TRUE	TRUE	5	2.32	2.31	2.35
10	10000	TRUE	FALSE	TRUE	10	2.45	2.47	2.57
12	10000	TRUE	FALSE	TRUE	5	2.63	2.64	2.66
14	10000	TRUE	FALSE	FALSE	10	2.53	2.53	2.57
16	10000	TRUE	FALSE	FALSE	5	2.68	2.68	2.66
18	10000	FALSE	TRUE	FALSE	5	2.46	2.46	2.45

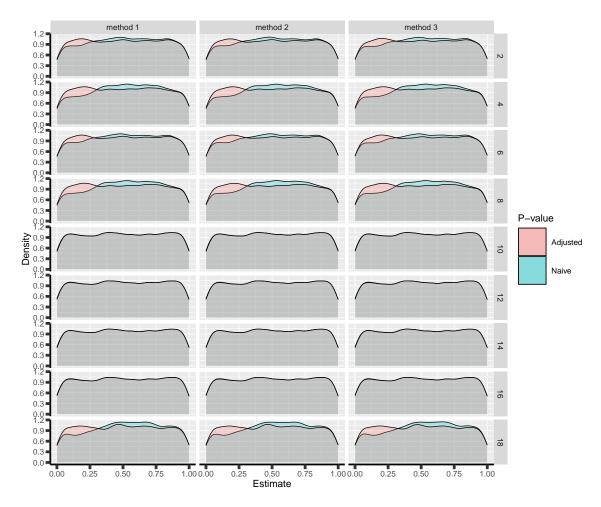


Figure 1: Naive and adjusted p-value distribution over all simulations under the null. Each row correspond to a different scenario

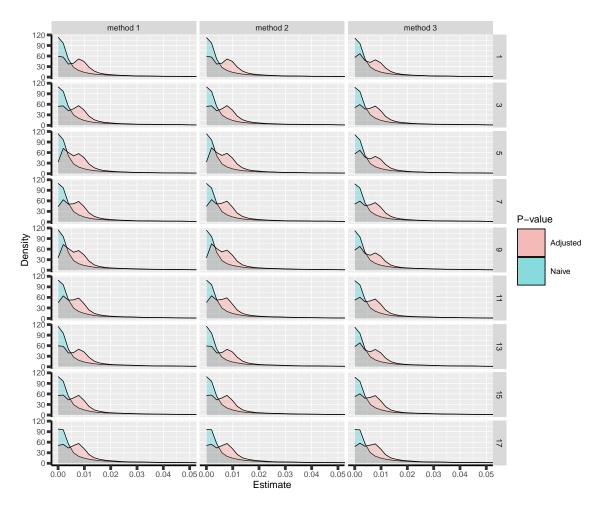


Figure 2: Naive and adjusted p-value distribution over all simulations under the alternative. Each row correspond to a different scenario

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	37.79	5.93	43.21	13.1
2:	10000	TRUE	typeI	TRUE	FALSE	10	0.80	71.13	1.62	26.5
3:	10000	TRUE	power	TRUE	FALSE	5	35.74	5.98	44.79	13.5
4:	10000	TRUE	typeI	TRUE	FALSE	5	0.74	69.32	1.66	28.3
5:	10000	TRUE	power	TRUE	TRUE	10	36.94	6.78	43.21	13.1
6:	10000	TRUE	typeI	TRUE	TRUE	10	0.62	71.31	1.62	26.5
7:	10000	TRUE	power	TRUE	TRUE	5	35.29	6.43	44.79	13.5
8:	10000	TRUE	typeI	TRUE	TRUE	5	0.66	69.40	1.66	28.3
9:	10000	TRUE	power	FALSE	TRUE	10	38.05	6.57	41.81	13.6
10:	10000	TRUE	typeI	FALSE	TRUE	10	0.61	0.20	1.84	97.4
11:	10000	TRUE	power	FALSE	TRUE	5	36.35	6.15	43.58	13.9
12:	10000	TRUE	typeI	FALSE	TRUE	5	0.70	0.06	1.93	97.3
13:	10000	TRUE	power	FALSE	FALSE	10	38.69	5.93	41.81	13.6
14:	10000	TRUE	typeI	FALSE	FALSE	10	0.69	0.12	1.84	97.4
15:	10000	TRUE	power	FALSE	FALSE	5	36.79	5.71	43.58	13.9
16:	10000	TRUE	typeI	FALSE	FALSE	5	0.75	0.01	1.93	97.3
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	37.85	6.19	43.08	12.9
2:	10000	TRUE	typeI	TRUE	FALSE	10	0.79	71.64	1.60	26.0
3:	10000	TRUE	power	TRUE	FALSE	5	35.77	5.99	44.76	13.5
4:	10000	TRUE	typeI	TRUE	FALSE	5	0.74	69.38	1.66	28.2
5:	10000	TRUE	power	TRUE	TRUE	10	36.69	6.24	43.66	13.4
6:	10000	TRUE	typeI	TRUE	TRUE	10	0.59	69.61	1.63	28.2
7:	10000	TRUE	power	TRUE	TRUE	5	35.02	6.05	45.18	13.8
8:	10000	TRUE	typeI	TRUE	TRUE	5	0.63	68.36	1.68	29.3
9:	10000	TRUE	power	FALSE	TRUE	10	37.85	6.04	42.27	13.8
10:	10000	TRUE	typeI	FALSE	TRUE	10	0.61	0.19	1.86	97.3
11:	10000	TRUE	power	FALSE	TRUE	5	36.18	5.84	43.86	14.1
12:	10000	TRUE	typeI	FALSE	TRUE	5	0.69	0.06	1.95	97.3
13:	10000	TRUE	power	FALSE	FALSE	10	38.70	6.09	41.74	13.5
14:	10000	TRUE	typeI	FALSE	FALSE	10	0.69	0.12	1.84	97.4
15:	10000	TRUE	power	FALSE	FALSE	5	36.82	5.75	43.54	13.9
16:	10000	TRUE	typeI	FALSE	FALSE	5	0.75	0.01	1.93	97.3
17:	10000	FALSE	power	TRUE	FALSE	5	34.03	5.36	46.27	14.3
18:	10000	FALSE	typeI	TRUE	FALSE	5	0.74	67.55	1.72	30.0

Method 3:

	N	missing	hypo	binding	fixC	ar	decision.eff	${\tt decision.fut}$	final.eff	<pre>final.fut</pre>
1:	10000	TRUE	power	TRUE	FALSE	10	40.58	6.53	39.85	13.0
2:	10000	TRUE	typeI	TRUE	FALSE	10	0.74	68.79	1.63	28.8
3:	10000	TRUE	power	TRUE	FALSE	5	36.54	6.30	43.60	13.6
4:	10000	TRUE	typeI	TRUE	FALSE	5	0.69	68.41	1.66	29.2
5:	10000	TRUE	power	TRUE	TRUE	10	40.58	6.53	39.85	13.0
6:	10000	TRUE	typeI	TRUE	TRUE	10	0.74	68.79	1.63	28.8
7:	10000	TRUE	power	TRUE	TRUE	5	36.54	6.30	43.60	13.6
8:	10000	TRUE	typeI	TRUE	TRUE	5	0.69	68.41	1.66	29.2
9:	10000	TRUE	power	FALSE	TRUE	10	41.34	6.20	38.92	13.5
10:	10000	TRUE	typeI	FALSE	TRUE	10	0.77	0.33	1.80	97.1
11:	10000	TRUE	power	FALSE	TRUE	5	37.71	6.03	42.35	13.9
12:	10000	TRUE	typeI	FALSE	TRUE	5	0.73	0.09	1.93	97.2
13:	10000	TRUE	power	FALSE	FALSE	10	41.34	6.20	38.92	13.5
14:	10000	TRUE	typeI	FALSE	FALSE	10	0.77	0.33	1.80	97.1
15:	10000	TRUE	power	FALSE	FALSE	5	37.71	6.03	42.35	13.9
16:	10000	TRUE	typeI	FALSE	FALSE	5	0.73	0.09	1.93	97.2
17:	10000	FALSE	power	TRUE	FALSE	5	34.65	5.59	45.27	14.5
18:	10000	FALSE	typeI	TRUE	FALSE	5	0.68	66.54	1.77	31.0

Relative frequency of stopping for with a threshold below 1.96: $\,$

	scenario	missing	method	binding	fixC	ar	hypo	N	rejection	rejectionBelow196
1:	1	TRUE	1	TRUE	FALSE	10	power	10000	81.00	0.85
2:	1	TRUE	2	TRUE	FALSE	10	power	10000	80.93	0.84
3:	1	TRUE	3	TRUE	FALSE	10	power	10000	80.43	0.00
4:	2	TRUE	1	TRUE	FALSE	10	typeI	10000	2.42	0.18
5:	2	TRUE	2	TRUE	FALSE	10	typeI	10000	2.39	0.17
6:	2	TRUE	3	TRUE	FALSE	10	typeI	10000	2.37	0.00
7:	3	TRUE	1	TRUE	FALSE	5	power	10000	80.53	0.45
8:	3	TRUE	2	TRUE	FALSE	5	power	10000	80.53	0.45
9:	3	TRUE	3	TRUE	FALSE	5	power	10000	80.14	0.00
10:	4	TRUE	1	TRUE	FALSE	5	typeI	10000	2.40	0.08
11:	4	TRUE	2	TRUE	FALSE	5	typeI	10000	2.40	0.08
12:	4	TRUE	3	TRUE	FALSE	5	typeI	10000	2.35	0.00
13:	5	TRUE	1	TRUE	TRUE	10	power	10000	80.15	0.00
14:	5	TRUE	2	TRUE	TRUE	10	power	10000	80.35	0.00
15:	5	TRUE	3	TRUE	TRUE	10	power	10000	80.43	0.00
16:	6	TRUE	1	TRUE	TRUE	10	typeI	10000	2.24	0.00
17:	6	TRUE	2	TRUE	TRUE	10	typeI	10000	2.22	0.00
18:	6	TRUE	3	TRUE	TRUE	10	typeI	10000	2.37	0.00
19:	7	TRUE	1	TRUE	TRUE	5	power	10000	80.08	0.00
20:	7	TRUE	2	TRUE	TRUE	5	power	10000	80.20	0.00
21:	7	TRUE	3	TRUE	TRUE	5	power	10000	80.14	0.00

22:	8	TRUE	1	TRUE	TRUE	5	typeI	10000	2.32	0.00
23:	8	TRUE	2	TRUE	TRUE	5	typeI	10000	2.31	0.00
24:	8	TRUE	3	TRUE	TRUE	5	typeI	10000	2.35	0.00
25:	9	TRUE	1	FALSE	TRUE	10	power	10000	79.86	0.00
26:	9	TRUE	2	FALSE	TRUE	10	power	10000	80.12	0.00
27:	9	TRUE	3	FALSE	TRUE	10	power	10000	80.26	0.00
28:	10	TRUE	1	FALSE	TRUE	10	typeI	10000	2.45	0.00
29:	10	TRUE	2	FALSE	TRUE	10	typeI	10000	2.47	0.00
30:	10	TRUE	3	FALSE	TRUE	10	typeI	10000	2.57	0.00
31:	11	TRUE	1	FALSE	TRUE	5	power	10000	79.93	0.00
32:	11	TRUE	2	FALSE	TRUE	5	power	10000	80.04	0.00
33:	11	TRUE	3	FALSE	TRUE	5	power	10000	80.06	0.00
34:	12	TRUE	1	FALSE	TRUE	5	typeI	10000	2.63	0.00
35:	12	TRUE	2	FALSE	TRUE	5	typeI	10000	2.64	0.00
36:	12	TRUE	3	FALSE	TRUE	5	typeI	10000	2.66	0.00
37:	13	TRUE	1	FALSE	FALSE	10	power	10000	80.50	0.64
38:	13	TRUE	2	FALSE	FALSE	10	power	10000	80.44	0.64
39:	13	TRUE	3	FALSE	FALSE	10	power	10000	80.26	0.00
40:	14	TRUE	1	FALSE	FALSE	10	typeI	10000	2.53	0.08
41:	14	TRUE	2	FALSE	FALSE	10	typeI	10000	2.53	0.08
42:	14	TRUE	3	FALSE	FALSE	10	typeI	10000	2.57	0.00
43:	15	TRUE	1	FALSE	FALSE	5	power	10000	80.37	0.44
44:	15	TRUE	2	FALSE	FALSE	5	power	10000	80.36	0.44
45:	15	TRUE	3	FALSE	FALSE	5	power	10000	80.06	0.00
46:	16	TRUE	1	FALSE	FALSE	5	typeI	10000	2.68	0.05
47:	16	TRUE	2	FALSE	FALSE	5	typeI	10000	2.68	0.05
48:	16	TRUE	3	FALSE	FALSE	5	typeI	10000	2.66	0.00
49:	17	FALSE	1	TRUE	FALSE	5	power	10000	80.31	0.42
50:	17	FALSE	2	TRUE	FALSE	5	power	10000	80.30	0.43
51:	17	FALSE	3	TRUE	FALSE	5	power	10000	79.92	0.00
52:	18	FALSE	1	TRUE	FALSE	5	typeI	10000	2.46	0.08
53:	18	FALSE	2	TRUE	FALSE	5	typeI	10000	2.46	0.08
54:	18	FALSE	3	TRUE	FALSE	5	typeI	10000	2.45	0.00

scenario missing method binding fixC ar hypo N rejection rejectionBelow196

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
                                     0.013450
                                               0.013150
                                                          0.014680
                                                                    0.005983
                                                                               0.005659
                                                                                         0.00218
 2: typeI
             TRUE
                     TRUE FALSE 10 -0.017939 -0.017844 -0.018560 -0.004484 -0.004412 -0.00508
 3: power
             TRUE
                     TRUE FALSE
                                  5
                                     0.022570
                                               0.022551
                                                          0.023584
                                                                    0.010450
                                                                              0.010477
                                                                                         0.00870
 4: typeI
                     TRUE FALSE
                                  5 -0.030342 -0.030312 -0.030651 -0.011844 -0.011798 -0.01238
             TRUE
                                                          0.014680
                                                                   0.001094 0.001687
 5: power
             TRUE
                     TRUE
                           TRUE 10
                                    0.013450 0.014032
                                                                                         0.00217
 6: typeI
             TRUE
                     TRUE
                           TRUE 10 -0.017939 -0.018711 -0.018560 -0.005373 -0.006062 -0.00508
7: power
             TRUE
                     TRUE
                           TRUE
                                  5
                                     0.022570 0.023089
                                                          0.023584
                                                                    0.007878
                                                                              0.008275
                                                                                         0.00870
                           TRUE
                                  5 -0.030342 -0.030850 -0.030651 -0.012252 -0.012829 -0.01238
 8: typeI
             TRUE
                     TRUE
 9: power
             TRUE
                    FALSE
                           TRUE 10
                                     0.014326
                                               0.014903
                                                          0.015285
                                                                    0.037532
                                                                              0.035615
                                                                                         0.03135
10: typeI
             TRUE
                    FALSE
                           TRUE 10
                                     0.000186
                                               0.000192
                                                          0.000511
                                                                    0.000991
                                                                               0.000981
                                                                                         0.00263
11: power
             TRUE
                    FALSE
                           TRUE
                                     0.023657
                                               0.024021
                                                          0.024379
                                                                    0.042787
                                  5
                                                                               0.041614
                                                                                         0.04039
                           TRUE
12: typeI
             TRUE
                    FALSE
                                 5
                                     0.000912
                                               0.000853
                                                          0.001008
                                                                    0.001112
                                                                              0.001062
                                                                                         0.00136
             TRUE
                    FALSE FALSE 10
                                                                    0.036631
13: power
                                     0.014326
                                               0.014160
                                                          0.015285
                                                                              0.037167
                                                                                         0.03139
                    FALSE FALSE 10
14: typeI
             TRUE
                                     0.000186
                                               0.000186
                                                          0.000511
                                                                    0.000793
                                                                               0.000783
                                                                                         0.00264
                    FALSE FALSE
                                     0.023657
                                               0.023651
15: power
             TRUE
                                  5
                                                          0.024379
                                                                    0.041744
                                                                               0.041949
                                                                                         0.04040
16: typeI
                                  5
                                     0.000912
                                                          0.001008
             TRUE
                    FALSE FALSE
                                               0.000912
                                                                    0.000964
                                                                               0.000962
                                                                                         0.00137
                                  5
                                     0.022836
                                               0.022775
                                                          0.023807
17: power
            FALSE
                     TRUE FALSE
                                                                    0.011971
                                                                               0.011956
                                                                                         0.01001
18: typeI
            FALSE
                     TRUE FALSE
                                  5 -0.029516 -0.029448 -0.029915 -0.011048 -0.011005 -0.01162
```

Median bias ² per estimator and method:

			-								
	hypo	missing	${\tt binding}$	fixC	ar	${\tt mbiasMLE1}$	${\tt mbiasMLE2}$	${\tt mbiasMLE3}$	${\tt mbiasMUE1}$	${\tt mbiasMUE2}$	mbiasMUE3
1:	power	TRUE	TRUE	FALSE	10	0.0261	0.0260	0.0301	-0.0024	-0.0025	-0.0054
2:	typeI	TRUE	TRUE	FALSE	10	-0.0173	-0.0170	-0.0202	0.0011	0.0009	-0.0001
3:	power	TRUE	TRUE	FALSE	5	0.0405	0.0405	0.0432	-0.0034	-0.0033	-0.0053
4:	typeI	TRUE	TRUE	FALSE	5	-0.0330	-0.0329	-0.0345	0.0007	0.0007	0.0008
5:	power	TRUE	TRUE	TRUE	10	0.0261	0.0265	0.0301	-0.0105	-0.0101	-0.0054
6:	typeI	TRUE	TRUE	TRUE	10	-0.0173	-0.0197	-0.0202	0.0011	-0.0006	-0.0001
7:	power	TRUE	TRUE	TRUE	5	0.0405	0.0407	0.0432	-0.0077	-0.0065	-0.0053
8:	typeI	TRUE	TRUE	TRUE	5	-0.0330	-0.0346	-0.0345	0.0007	0.0009	0.0008
9:	power	TRUE	FALSE	TRUE	10	0.0326	0.0332	0.0327	0.0390	0.0345	0.0277
10:	typeI	TRUE	FALSE	TRUE	10	-0.0009	-0.0009	-0.0009	-0.0008	-0.0008	0.0014
11:	power	TRUE	FALSE	TRUE	5	0.0462	0.0459	0.0489	0.0338	0.0315	0.0294
12:	typeI	TRUE	FALSE	TRUE	5	-0.0009	-0.0010	-0.0009	-0.0008	-0.0010	0.0003
13:	power	TRUE	FALSE	FALSE	10	0.0326	0.0324	0.0327	0.0390	0.0403	0.0277
14:	typeI	TRUE	FALSE	FALSE	10	-0.0009	-0.0009	-0.0009	-0.0008	-0.0008	0.0014
15:	power	TRUE	FALSE	FALSE	5	0.0462	0.0464	0.0489	0.0337	0.0342	0.0294
16:	typeI	TRUE	FALSE	FALSE	5	-0.0009	-0.0009	-0.0009	-0.0008	-0.0008	0.0003
17:	power	FALSE	TRUE	FALSE	5	0.0383	0.0383	0.0400	-0.0026	-0.0025	-0.0047
18:	typeI	FALSE	TRUE	FALSE	5	-0.0329	-0.0327	-0.0353	0.0044	0.0044	0.0035

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:

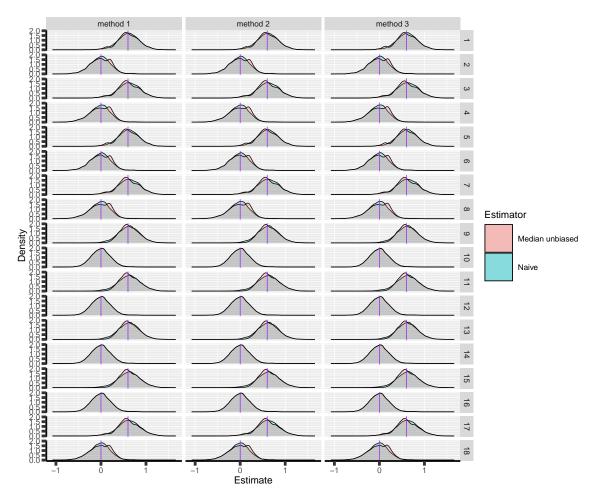


Figure 3: Naive and Median unbiased estimate distribution over all simulations. Each row correspond to a different scenario

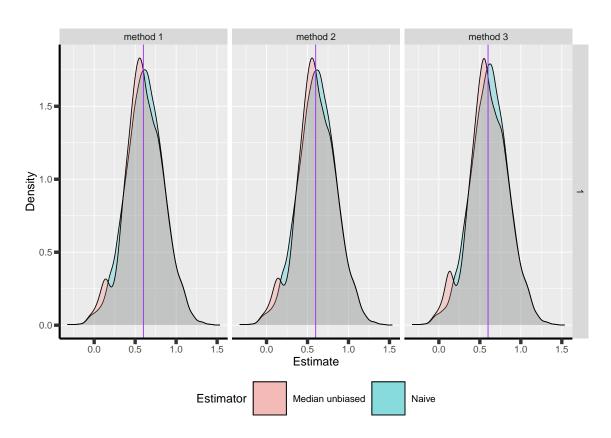


Figure 4: Same but specific to scenario 1

Distribution of the median unbiased estimate conditional to the stage:

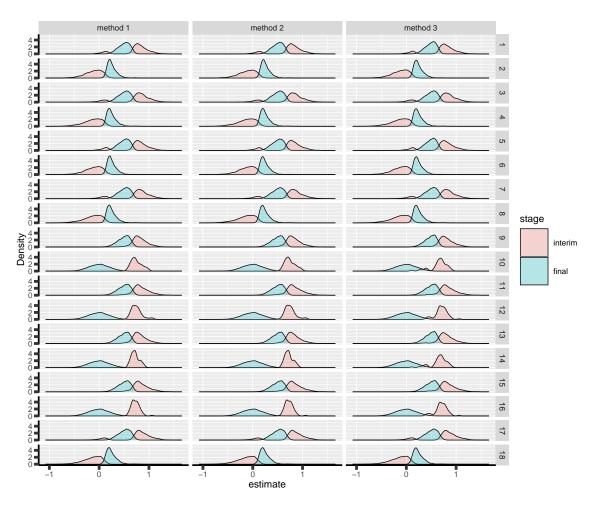


Figure 5: Median unbiased estimate distribution conditional to the stage. Each row correspond to a different scenario.

5 Special cases

Reason for stopping (efficacy, futility, Imax reached), continuing the trial (decreasing information, no boundary crossed), or concluding (stop for futility at interim):

		scenario	1	2	3	4	5	6	7	8	ľ
reason	method										ļ
decreasing information	1		0	0	1	1	0	0	1	1	ļ
	2		0	0	1	1	0	0	1	1	ľ
	3		0	0	1	1	0	0	1	1	ļ
efficacy	1		3739	81	3573	74	3739	81	3573	74	ľ
	2		3744	81	3576	74	3718	79	3545	71	ľ
	3		4165	108	3721	82	4165	108	3721	82	ļ
futility	1		632	7111	599	6932	632	7111	599	6932	ļ
	2		659	7161	600	6938	574	6940	562	6828	ļ
	3		545	6844	563	6828	545	6844	563	6828	ļ
Imax reached	1		1	1	0	0	1	1	0	0	ļ
	2		1	1	0	0	1	1	0	0	ļ
	3		1	1	0	0	1	1	0	0	ľ
no boundary crossed	1		5628	2807	5828	2994	5628	2807	5828	2994	ļ
	2		5596	2757	5824	2988	5707	2980	5893	3101	ŀ
	3		5289	3047	5716	3090	5289	3047	5716	3090	ļ
stop for futility at interim	1		0	0	0	0	0	0	0	0	
-	2		0	0	0	0	0	0	0	0	
	3		11	1	2	0	11	1	2	0	
			0	10	4.4	10	40	4.4	4.5	1.0	47
	51	scenario	9	10	11	12	13	14	15	16	17
reason	method		2240	04	0.000	7.0	2240	04	2200	70	2226
efficacy	1		3849		3680		3849		3680		3396
	2		3829		3661		3850		3683		3400
	3		4238		3831		4238		3831		3528
futility	1			7122		6945		7122		6945	535 6
	2			6975		6838		7164		6950	539 6
_	3			6890		6842		6890		6842	496 6
no boundary crossed	1										6069 3
	2										6061 3
	3										5976 3
stop for futility at interim	1		0	0	0	0	0	0	0	0	0
	2		0	0	0	0	0	0	0	0	0
	3		8	0	0	0	8	0	0	0	1

6 Reversal probability

Percentage of time we observe a reversal:

	N	hypo	missing	ar	binding	fixC	fu2eff_1	fu2eff_2	$fu2eff_3$	$eff2fu_1$	${\tt eff2fu_2}$	eff2fu_3
1:	10000	power	TRUE	10	TRUE	FALSE	0.57	0.61	0	0.17	0.20	1.07
2:	10000	typeI	TRUE	10	TRUE	FALSE	0.10	0.09	0	0.11	0.11	0.34
3:	10000	power	TRUE	5	TRUE	FALSE	0.08	0.08	0	0.07	0.07	0.67
4:	10000	typeI	TRUE	5	TRUE	FALSE	0.02	0.02	0	0.02	0.02	0.13
5:	10000	power	TRUE	10	TRUE	TRUE	0.22	0.16	0	0.67	0.65	1.07
6:	10000	typeI	TRUE	10	TRUE	TRUE	0.02	0.01	0	0.21	0.21	0.34
7:	10000	power	TRUE	5	TRUE	TRUE	0.02	0.02	0	0.46	0.45	0.67
8:	10000	typeI	TRUE	5	TRUE	TRUE	0.00	0.00	0	0.08	0.08	0.13
9:	10000	power	TRUE	10	FALSE	TRUE	0.14	0.11	0	0.58	0.55	1.04
10:	10000	typeI	TRUE	10	FALSE	TRUE	0.00	0.00	0	0.20	0.19	0.33
11:	10000	power	TRUE	5	FALSE	TRUE	0.01	0.01	0	0.46	0.44	0.60
12:	10000	typeI	TRUE	5	FALSE	TRUE	0.00	0.00	0	0.06	0.06	0.09
13:	10000	power	TRUE	10	FALSE	FALSE	0.41	0.42	0	0.21	0.22	1.04
14:	10000	typeI	TRUE	10	FALSE	FALSE	0.00	0.00	0	0.12	0.12	0.33
15:	10000	power	TRUE	5	FALSE	FALSE	0.03	0.03	0	0.04	0.04	0.60
16:	10000	typeI	TRUE	5	FALSE	FALSE	0.00	0.00	0	0.01	0.01	0.09
17:	10000	power	FALSE	5	TRUE	FALSE	0.06	0.07	0	0.04	0.04	0.63
18:	10000	typeI	FALSE	5	TRUE	FALSE	0.01	0.01	0	0.01	0.01	0.12

7 Logical consistency of p-values/CIs

7.1 Mismatch p-value / boundaries

When concluding for futility:

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

When concluding for efficacy:

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

7.2 Mismatch confidence intervals / boundaries

When concluding for futility:

```
hypo missing ar binding fixC method 1 method 2 method 3
             TRUE 10
                        TRUE FALSE
                                          0
                                                   0 0.0000000
 1: power
 2: typeI
             TRUE 10
                        TRUE FALSE
                                          0
                                                   0 0.000000
3: power
             TRUE 5
                        TRUE FALSE
                                          0
                                                   0 0.0000000
4: typeI
             TRUE 5
                        TRUE FALSE
                                          0
                                                   0 0.0000000
5: power
             TRUE 10
                        TRUE
                             TRUE
                                          0
                                                   0 0.000000
6: typeI
             TRUE 10
                        TRUE TRUE
                                          0
                                                   0 0.0000000
7: power
             TRUE 5
                        TRUE TRUE
                                          0
                                                   0 0.0000000
8: typeI
            TRUE 5
                        TRUE
                             TRUE
                                          0
                                                   0 0.0000000
9: power
            TRUE 10
                       FALSE TRUE
                                                   0 7.8484438
                                          0
10: typeI
             TRUE 10
                       FALSE
                             TRUE
                                          0
                                                   0 0.1747533
11: power
             TRUE 5
                       FALSE
                             TRUE
                                          0
                                                   0 4.1322314
12: typeI
             TRUE 5
                       FALSE TRUE
                                          0
                                                   0 0.0821946
13: power
             TRUE 10
                       FALSE FALSE
                                          0
                                                   0 7.8484438
14: typeI
             TRUE 10
                       FALSE FALSE
                                          0
                                                   0 0.1747533
15: power
             TRUE 5
                       FALSE FALSE
                                          0
                                                   0 4.1322314
16: typeI
             TRUE 5
                       FALSE FALSE
                                          0
                                                   0 0.0821946
17: power
            FALSE 5
                        TRUE FALSE
                                          0
                                                   0 0.0000000
18: typeI
            FALSE 5
                        TRUE FALSE
                                          0
                                                   0 0.0000000
```

This only occurs for non-binding futility rules and concluding futility, e.g.: When concluding for efficacy:

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

7.3 Range of p-values

	missing	binding	fixC	ar	hypo	method 1	method 2	method 3
1:	TRUE	TRUE	FALSE	10	power	[0;0.9147]	[0;0.9147]	[0;0.9147]
2:	TRUE	TRUE	FALSE	10	typeI	[1e-04;0.9999]	[1e-04;0.9999]	[1e-04;0.9999]
3:	TRUE	TRUE	FALSE	5	power	[0;0.9015]	[0;0.9015]	[0;0.9015]
4:	TRUE	TRUE	FALSE	5	typeI	[1e-04;0.9998]	[1e-04;0.9998]	[1e-04;0.9998]
5:	TRUE	TRUE	TRUE	10	power	[7e-04;0.9147]	[7e-04;0.9147]	[0;0.9147]
6:	TRUE	TRUE	TRUE	10	typeI	[0.0016;0.9999]	[0.0016;0.9999]	[1e-04;0.9999]
7:	TRUE	TRUE	TRUE	5	power	[1e-04;0.9015]	[1e-04;0.9015]	[0;0.9015]
8:	TRUE	TRUE	TRUE	5	typeI	[5e-04;0.9998]	[5e-04;0.9998]	[1e-04;0.9998]
9:	TRUE	FALSE	TRUE	10	power	[8e-04;1]	[8e-04;1]	[0;1]
10:	TRUE	FALSE	TRUE	10	typeI	[0.0015;1]	[0.0015;1]	[5e-04;1]
11:	TRUE	FALSE	TRUE	5	power	[1e-04;1]	[1e-04;1]	[0;1]
12:	TRUE	FALSE	TRUE	5	typeI	[6e-04;1]	[5e-04;1]	[2e-04;1]
13:	TRUE	FALSE	FALSE	10	power	[0;1]	[0;1]	[0;1]
14:	TRUE	FALSE	FALSE	10	typeI	[1e-04;1]	[1e-04;1]	[5e-04;1]
15:	TRUE	FALSE	FALSE	5	power	[0;1]	[0;1]	[0;1]
16:	TRUE	FALSE	FALSE	5	typeI	[0;1]	[0;1]	[2e-04;1]
17:	FALSE	TRUE	FALSE	5	power	[0;0.9642]	[0;0.9642]	[0;0.9642]
18:	FALSE	TRUE	FALSE	5	typeI	[0;1]	[0;1]	[3e-04;1]

8 Coverage

```
hypo missing ar binding fixC method 1 method 2 method 3
            FALSE 5
                        TRUE FALSE 94.79000 94.79000 94.92000
 1: power
 2: power
             TRUE 5
                       FALSE FALSE 95.86382 95.86207 95.66505
3: power
             TRUE 5
                       FALSE TRUE 96.30458 96.26486 95.66505
 4: power
             TRUE 5
                        TRUE FALSE 94.74000 94.74000 94.87000
5: power
             TRUE 5
                        TRUE
                             TRUE 95.08000 95.08000 94.87000
 6: power
             TRUE 10
                       FALSE FALSE 95.98172 96.04941 95.75968
7: power
             TRUE 10
                       FALSE
                             TRUE 96.79139 96.75297 95.75968
             TRUE 10
8: power
                        TRUE FALSE 94.84000 94.82000 95.12000
             TRUE 10
                        TRUE TRUE 95.73000 95.65000 95.12000
9: power
10: typeI
            FALSE 5
                        TRUE FALSE 95.14000 95.14000 95.15000
                       FALSE FALSE 94.86949 94.86949 95.39954
11: typeI
             TRUE 5
             TRUE 5
                       FALSE
                             TRUE 94.91695 94.90745 95.39954
12: typeI
13: typeI
             TRUE 5
                        TRUE FALSE 94.82000 94.82000 94.87000
14: typeI
             TRUE 5
                             TRUE 94.90000 94.91000 94.87000
15: typeI
             TRUE 10
                       FALSE FALSE 95.01402 95.01402 96.04407
             TRUE 10
                             TRUE 95.09116 95.07162 96.04407
16: typeI
                       FALSE
17: typeI
             TRUE 10
                        TRUE FALSE 95.16000 95.19000 95.21000
             TRUE 10
                        TRUE TRUE 95.34000 95.36000 95.21000
18: typeI
```

Average width of the confidence intervals

```
hypo missing ar binding fixC method 1 method 2 method 3
 1: power
            FALSE 5
                        TRUE FALSE 1.0517981 1.0518066 1.053592
 2: power
            TRUE 5
                       FALSE FALSE 1.0355785 1.0355525 1.030753
 3: power
             TRUE 5
                       FALSE TRUE 1.0410966 1.0414270 1.030753
            TRUE 5
4: power
                        TRUE FALSE 1.0513207 1.0513607 1.052634
5: power
            TRUE 5
                        TRUE
                             TRUE 1.0570088 1.0563598 1.052629
 6: power
            TRUE 10
                       FALSE FALSE 1.0469276 1.0468858 1.039428
7: power
            TRUE 10
                       FALSE
                             TRUE 1.0634581 1.0625586 1.039438
8: power
            TRUE 10
                        TRUE FALSE 1.0624494 1.0626858 1.062576
            TRUE 10
                             TRUE 1.0765867 1.0753692 1.062555
9: power
10: typeI
            FALSE 5
                        TRUE FALSE 1.0431774 1.0431218 1.046821
                       FALSE FALSE 0.9997886 0.9998440 1.018905
11: typeI
            TRUE
                  5
            TRUE 5
                       FALSE TRUE 0.9996979 0.9996859 1.018905
12: typeI
            TRUE 5
                        TRUE FALSE 1.0416221 1.0415882 1.045180
13: typeI
            TRUE 5
                             TRUE 1.0416986 1.0423673 1.045180
14: typeI
                        TRUE
15: typeI
            TRUE 10
                       FALSE FALSE 1.0182710 1.0227130 1.049875
16: typeI
            TRUE 10
                             TRUE 1.0183637 1.0101640 1.049882
                       FALSE
17: typeI
             TRUE 10
                        TRUE FALSE 1.0459447 1.0453954 1.056218
            TRUE 10
                             TRUE 1.0461003 1.0478314 1.056215
18: typeI
                        TRUE
```

Average ratio between the length of the MUE CIs vs. the ML CIs

```
hypo missing ar binding fixC method 1 method 2 method 3
                  5
 1: power
            FALSE
                        TRUE FALSE 1.0554164 1.0554324 1.057018
             TRUE 5
                       FALSE FALSE 1.0477000 1.0477317 1.043003
 2: power
             TRUE 5
                       FALSE TRUE 1.0532445 1.0529897 1.043003
 3: power
             TRUE 5
                       TRUE FALSE 1.0556658 1.0557135 1.056796
 4: power
 5: power
             TRUE 5
                        TRUE TRUE 1.0607293 1.0599867 1.056792
 6: power
             TRUE 10
                       FALSE FALSE 1.0539283 1.0540501 1.045799
             TRUE 10
                       FALSE TRUE 1.0695786 1.0683330 1.045809
 7: power
8: power
             TRUE 10
                        TRUE FALSE 1.0641965 1.0644562 1.064036
             TRUE 10
                        TRUE TRUE 1.0773006 1.0760174 1.064016
 9: power
            FALSE 5
10: typeI
                       TRUE FALSE 1.0496649 1.0496083 1.053799
             TRUE
11: typeI
                  5
                       FALSE FALSE 0.9997633 0.9998237 1.019473
             TRUE 5
                       FALSE TRUE 0.9998075 0.9997468 1.019473
12: typeI
             TRUE 5
13: typeI
                        TRUE FALSE 1.0486330 1.0486034 1.052752
             TRUE 5
14: typeI
                        TRUE TRUE 1.0487063 1.0493717 1.052752
             TRUE 10
                       FALSE FALSE 1.0194380 1.0240187 1.051009
15: typeI
             TRUE 10
16: typeI
                       FALSE TRUE 1.0196328 1.0111242 1.051015
17: typeI
             TRUE 10
                        TRUE FALSE 1.0497075 1.0491459 1.060913
             TRUE 10
                        TRUE TRUE 1.0498579 1.0516113 1.060910
18: typeI
```

9 Percentage of missing values

At the first interim

- pc.all percentage of observations with full data (with respect to all observations, i.e. patients with baseline measurement)
- 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

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

	method	missing	ar	hypo	fixC	binding	N	pc.all	pc.missing3	pc.missing23
1:	1	TRUE	5	power	FALSE	TRUE	10000	79.52088	9.591086	10.888036
2:	1	TRUE	5	typeI	FALSE	TRUE	10000	79.52088	9.591086	10.888036
3:	1	TRUE	5	power	TRUE	TRUE	10000	79.52088	9.591086	10.888036
4:	1	TRUE	5	typeI	TRUE	TRUE	10000	79.52088	9.591086	10.888036
5:	1	TRUE	5	power	TRUE	FALSE	10000	79.64470	9.441772	10.913523
6:	1	TRUE	5	typeI	TRUE	FALSE	10000	79.64470	9.441772	10.913523
7:	1	TRUE	5	power	FALSE	FALSE	10000	79.64470	9.441772	10.913523
8:	1	TRUE	5	typeI	FALSE	FALSE	10000	79.64470	9.441772	10.913523
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	71.59741	13.353880	15.048710
12:	1	TRUE	10	typeI	FALSE	TRUE	10000	71.59741	13.353880	15.048710
13:	1	TRUE	10	power	TRUE	TRUE	10000	71.59741	13.353880	15.048710
14:	1	TRUE	10	typeI	TRUE	TRUE	10000	71.59741	13.353880	15.048710
15:	1	TRUE	10	power	TRUE	FALSE	10000	71.79650	13.161615	15.041889
16:	1	TRUE	10	typeI	TRUE	FALSE	10000	71.79650	13.161615	15.041889
17:	1	TRUE	10	power	FALSE	FALSE	10000	71.79650	13.161615	15.041889
18:	1	TRUE	10	typeI	FALSE	FALSE	10000	71.79650	13.161615	15.041889

10 Information

Percentage of information for method 1^3 :

```
scenario missing binding fixC ar interim decision
                                                        final
            TRUE
                    TRUE FALSE 10 54.63712 75.34460 102.69691
       1
      2
            TRUE
                    TRUE FALSE 10 54.63712 74.98217 102.36588
      3
                    TRUE FALSE 5 53.26864 64.03618 102.73604
            TRUE
      4
                    TRUE FALSE 5 53.26864 63.58436 102.37416
            TRUE
      5
            TRUE
                    TRUE
                          TRUE 10 54.63712 75.34460 102.69691
                          TRUE 10 54.63712 74.98217 102.36588
      6
            TRUE
                    TRUE
      7
                                5 53.26864 64.03618 102.73604
            TRUE
                    TRUE
                          TRUE
                          TRUE 5 53.26864 63.58436 102.37416
      8
            TRUE
                    TRUE
                          TRUE 10 54.50012 74.96442 102.53821
      9
            TRUE
                   FALSE
                   FALSE
                          TRUE 10 54.50012 75.17490 103.12700
      10
            TRUE
                          TRUE
                                5 53.15854 63.71662 102.62539
      11
            TRUE
                   FALSE
      12
            TRUE
                   FALSE
                          TRUE
                                5 53.15854 64.60960 103.12516
                   FALSE FALSE 10 54.50012 74.96442 102.53821
      13
            TRUE
            TRUE
                   FALSE FALSE 10 54.50012 75.17490 103.12700
      14
                   FALSE FALSE 5 53.15854 63.71662 102.62539
            TRUE
      15
                   FALSE FALSE 5 53.15854 64.60960 103.12516
      16
            TRUE
      17
           FALSE
                    TRUE FALSE 5 52.06840 63.77019 99.96969
                    TRUE FALSE 5 52.06840 63.21929 99.62860
      18
           FALSE
```

Similar results for other methods.

³average over the reached stages