Results simulation study DelayedGSD

January 19, 2023

1 Rejection rate

Power by method (columns) and scenario (rows): (nominal level 0.8)

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)

```
tablePrintH0 <- dcast(res2stageS.rejection[hypo=="typeI"],
                scenario + N + missing + binding + fixC + ar ~ method.
   char,
                value.var = "rejectionRate")
print(tablePrintH0, row.names = FALSE)
```

scenario	N	missing	binding	fixC	ar	method 1	method 2	method 3
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	2.09	2.09	2.26
12	10000	TRUE	FALSE	TRUE	5	2.30	2.28	2.33
14	10000	TRUE	FALSE	FALSE	10	2.29	2.28	2.46
16	10000	TRUE	FALSE	FALSE	5	2.38	2.37	2.46
18	10000	FALSE	TRUE	FALSE	5	2.46	2.44	2.45

⚠ slightly too lower type 1 error for some scenario

2 Conclusion of the trial

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

- Method 1

	N	missing	hypo	binding	fixC	ar	decision.eff	decision.fut	final.eff	final.fut
1:	10000	TRUE	power	TRUE	FALSE	10	37.82	6.050	43.18	13.0
2:	10000	TRUE	typeI	TRUE	FALSE	10	0.79	70.850	1.67	26.7
3:	10000	TRUE	power	TRUE	FALSE	5	35.60	6.020	45.00	13.4
4:	10000	TRUE	typeI	TRUE	FALSE	5	0.68	69.210	1.74	28.4
5:	10000	TRUE	power	TRUE	TRUE	10	36.45	6.530	43.36	13.7
6:	10000	TRUE	typeI	TRUE	TRUE	10	0.64	71.290	1.61	26.5
7:	10000	TRUE	power	TRUE	TRUE	5	34.68	5.860	45.32	14.1
8:	10000	TRUE	typeI	TRUE	TRUE	5	0.72	69.110	1.70	28.5
9:	10000	TRUE	power	FALSE	TRUE	10	37.57	6.630	42.93	12.9
10:	2870	TRUE	typeI	FALSE	TRUE	10	1.99	0.976	5.30	91.7
11:	10000	TRUE	power	FALSE	TRUE	5	36.02	6.280	44.71	13.0
12:	3043	TRUE	typeI	FALSE	TRUE	5	2.40	0.296	5.16	92.1
13:	10000	TRUE	power	FALSE	FALSE	10	38.32	5.870	42.35	13.5
14:	2874	TRUE	typeI	FALSE	FALSE	10	2.40	0.313	5.57	91.7
15:	10000	TRUE	power	FALSE	FALSE	5	36.75	5.700	43.90	13.6
16:	3080	TRUE	typeI	FALSE	FALSE	5	2.18	0.000	5.55	92.3
17:	10000	FALSE	power	TRUE	FALSE	5	33.98	5.330	46.33	14.4
18:	10000	FALSE	typeI	TRUE	FALSE	5	0.74	67.480	1.72	30.1

⚠ something is not quite right for non-binding scenarios under the null (N should be 10000).

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	6.2200	43.13	13.0
2:	10000	TRUE	typeI	TRUE	FALSE	10	0.85	71.1800	1.68	26.3
3:	10000	TRUE	power	TRUE	FALSE	5	35.55	6.1000	44.90	13.5
4:	10000	TRUE	typeI	TRUE	FALSE	5	0.67	69.0500	1.74	28.5
5:	10000	TRUE	power	TRUE	TRUE	10	36.82	5.9400	43.59	13.6
6:	10000	TRUE	typeI	TRUE	TRUE	10	0.63	70.0200	1.62	27.7
7:	10000	TRUE	power	TRUE	TRUE	5	35.06	5.6300	45.40	13.9
8:	10000	TRUE	typeI	TRUE	TRUE	5	0.71	68.4600	1.68	29.1
9:	10000	TRUE	power	FALSE	TRUE	10	37.76	6.2100	43.09	12.9
10:	2956	TRUE	typeI	FALSE	TRUE	10	1.89	0.8796	5.18	92.1
11:	10000	TRUE	power	FALSE	TRUE	5	36.07	6.1000	44.75	13.1
12:	3093	TRUE	typeI	FALSE	TRUE	5	2.33	0.2263	5.04	92.4
13:	10000	TRUE	power	FALSE	FALSE	10	38.33	6.1100	42.27	13.3
14:	2820	TRUE	typeI	FALSE	FALSE	10	2.45	0.3191	5.64	91.6
15:	10000	TRUE	power	FALSE	FALSE	5	36.78	5.7200	43.86	13.6
16:	3075	TRUE	typeI	FALSE	FALSE	5	2.15	0.0325	5.56	92.3
17:	10000	FALSE	power	TRUE	FALSE	5	33.68	5.1700	46.60	14.5
18:	10000	FALSE	typeI	TRUE	FALSE	5	0.72	67.4200	1.72	30.1

⚠ something is not quite right for non-binding scenarios under the null (N should be 10000).

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         6.540     40.01      13.0
 2: 10000    TRUE typeI    TRUE FALSE 10         0.74        68.770      1.66      28.8
 3: 10000    TRUE power    TRUE FALSE  5        36.49         6.420     43.72      13.4
 4: 10000    TRUE typeI    TRUE FALSE  5         0.68        68.370      1.72      29.2
 5: 10000    TRUE power    TRUE  TRUE 10        39.85         5.830     40.54      13.8
 6: 10000    TRUE typeI    TRUE  TRUE 10         0.73        68.890      1.72      28.7
 7: 10000    TRUE power    TRUE  TRUE  5        35.70         5.810     44.38      14.1
 8: 10000    TRUE typeI    TRUE  TRUE  5         0.78        68.260      1.72      29.2
 9: 10000    TRUE power   FALSE  TRUE 10        41.03         6.390     39.88      12.7
10:  3086    TRUE typeI   FALSE  TRUE 10         2.33         1.231      4.99      91.4
11: 10000    TRUE power   FALSE  TRUE  5        37.08         6.140     43.67      13.1
12:  3133    TRUE typeI   FALSE  TRUE  5         2.36         0.447      5.08      92.1
13: 10000    TRUE power   FALSE FALSE 10        41.47         6.050     39.18      13.3
14:  3130    TRUE typeI   FALSE FALSE 10         2.59         0.990      5.27      91.2
15: 10000    TRUE power   FALSE FALSE  5        37.37         5.860     43.09      13.7
16:  3163    TRUE typeI   FALSE FALSE  5         2.37         0.253      5.41      92.0
17: 10000   FALSE power    TRUE FALSE  5        34.66         5.580     45.27      14.5
18: 10000   FALSE typeI    TRUE FALSE  5         0.68        66.540      1.77      31.0
```

⚠ something is not quite right for non-binding scenarios under the null (`N` should be 10000).

3 Bias

True effect: 0.6 Bias per estimator and method:

	hypo	missing	binding	fixC	ar	biasMLE1	biasMLE2	biasMLE3	biasMUE1	biasMUE2	biasMUE3
1:	power	TRUE	TRUE	FALSE	10	0.0130	0.0131	0.0141	-0.0023	-0.0017	-0.0042
2:	typeI	TRUE	TRUE	FALSE	10	-0.0184	-0.0184	-0.0185	0.0002	-0.0013	0.0001
3:	power	TRUE	TRUE	FALSE	5	0.0224	0.0222	0.0234	-0.0030	-0.0016	-0.0018
4:	typeI	TRUE	TRUE	FALSE	5	-0.0304	-0.0308	-0.0306	0.0000	-0.0002	0.0001
5:	power	TRUE	TRUE	TRUE	10	0.0116	0.0121	0.0130	-0.0053	-0.0061	-0.0080
6:	typeI	TRUE	TRUE	TRUE	10	-0.0221	-0.0223	-0.0223	-0.0113	-0.0079	-0.0099
7:	power	TRUE	TRUE	TRUE	5	0.0216	0.0220	0.0227	-0.0073	-0.0075	-0.0075
8:	typeI	TRUE	TRUE	TRUE	5	-0.0339	-0.0344	-0.0341	-0.0105	-0.0081	-0.0105
9:	power	TRUE	FALSE	TRUE	10	0.0150	0.0151	0.0163	-0.0025	-0.0044	-0.0036
10:	typeI	TRUE	FALSE	TRUE	10	0.1776	0.1740	0.1713	0.3606	0.3562	0.3487
11:	power	TRUE	FALSE	TRUE	5	0.0242	0.0242	0.0252	-0.0014	-0.0012	-0.0026
12:	typeI	TRUE	FALSE	TRUE	5	0.1722	0.1701	0.1700	0.3413	0.3432	0.3382
13:	power	TRUE	FALSE	FALSE	10	0.0144	0.0141	0.0157	-0.0033	-0.0036	0.0012
14:	typeI	TRUE	FALSE	FALSE	10	0.1803	0.1821	0.1736	0.3612	0.3628	0.3508
15:	power	TRUE	FALSE	FALSE	5	0.0234	0.0233	0.0243	-0.0010	-0.0010	-0.0028
16:	typeI	TRUE	FALSE	FALSE	5	0.1721	0.1720	0.1705	0.3455	0.3452	0.3416
17:	power	FALSE	TRUE	FALSE	5	0.0228	0.0228	0.0238	-0.0026	-0.0008	-0.0038
18:	typeI	FALSE	TRUE	FALSE	5	-0.0295	-0.0297	-0.0299	0.0044	0.0031	0.0035

⚠ clear bias for non-binding scenarios under the null

4 Distribution of the estimates

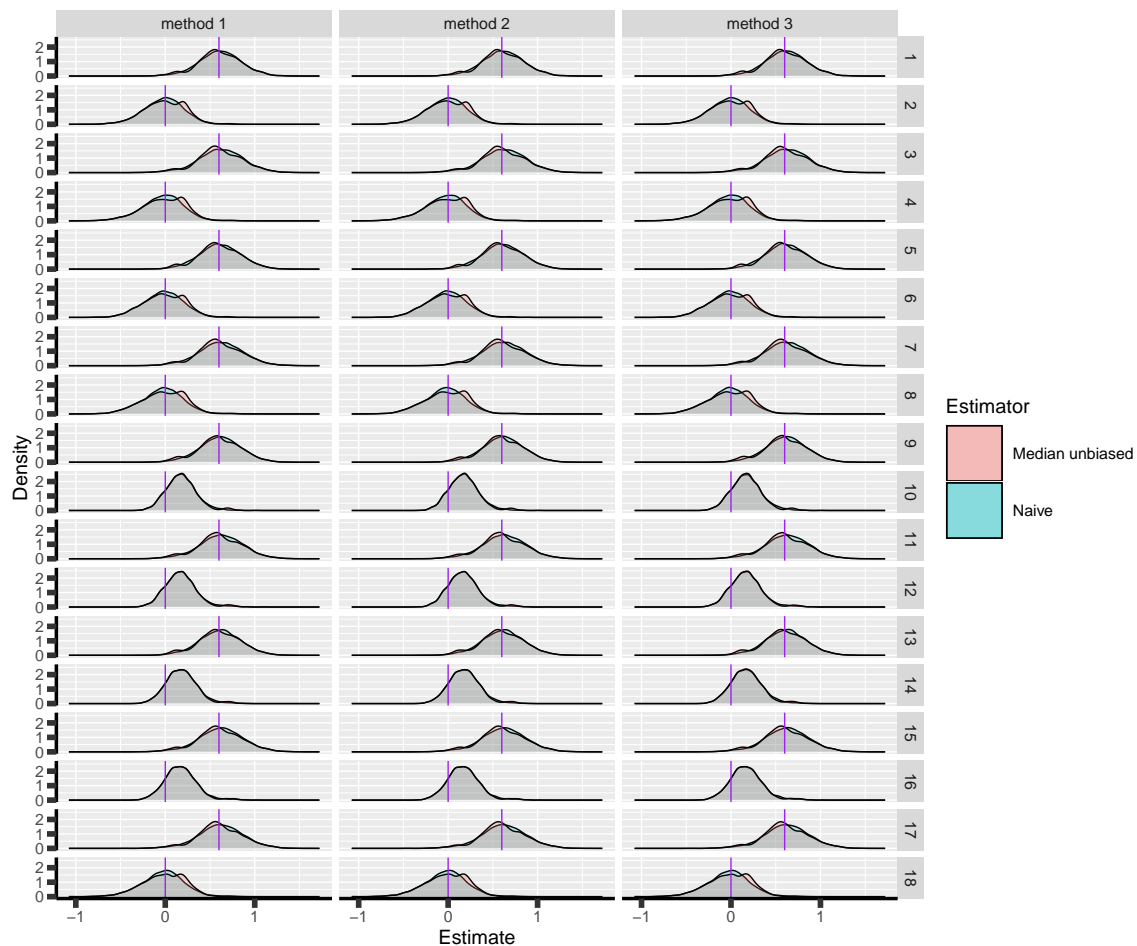Distribution of the estimates:

Figure 1: Naive and Median unbiased estimate distribution over all simulations. Each row correspond to a different scenario
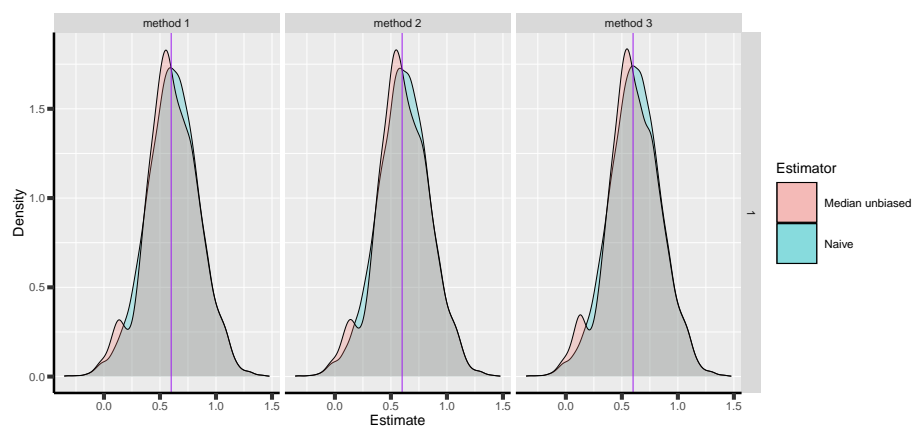

Figure 2: Same but specific to scenario 1

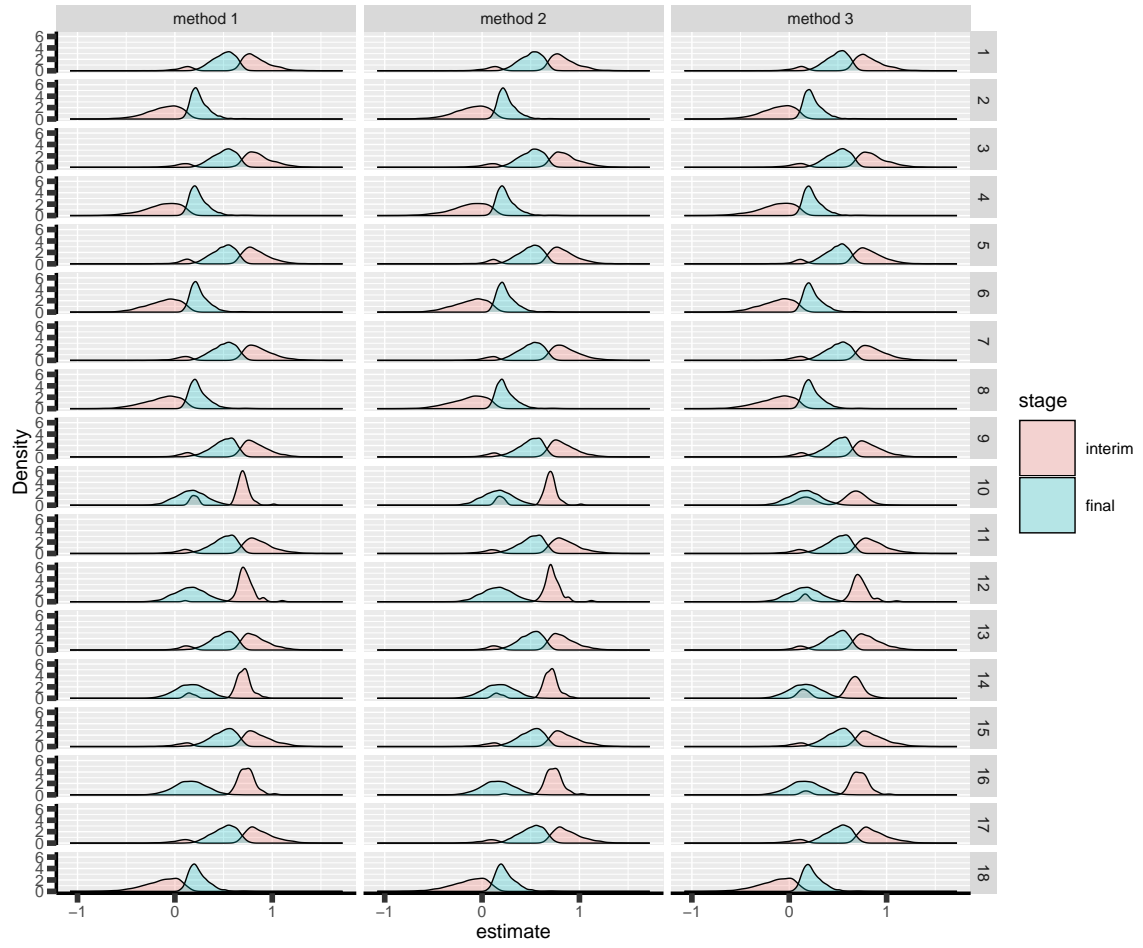Distribution of the median unbiased estimate conditional to the stage:

Figure 3: 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):

reason	method	scenario 1	2	3	4	5	6	7	8
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	77	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

reason	method	scenario 9	10	11	12	13	14	15	16
decreasing information	1	0	0	1	0	0	0	0	0
	2	0	0	1	0	0	0	0	0
	3	0	0	1	0	0	0	0	0
efficacy	1	3805	84	3634	82	3815	78	3674	67
	2	3824	81	3646	79	3816	78	3677	67
	3	4206	109	3761	88	4238	112	3788	83
futility	1	614	7130	596	6957	604	7126	571	6920
	2	572	7044	571	6907	628	7180	573	6925
	3	535	6914	561	6867	514	6870	535	6837
Imax reached	1	1	1	0	0	0	0	0	0
	2	1	1	0	0	0	0	0	0
	3	1	1	0	0	0	0	0	0
no boundary crossed	1	5580	2785	5770	2961	5581	2796	5755	3013
	2	5603	2874	5783	3014	5556	2742	5750	3008
	3	5258	2976	5678	3045	5248	3018	5677	3080

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 0.39860488
 2: power    TRUE  5   FALSE FALSE 0.41343669 0.41322314 0.46059365
 3: power    TRUE  5   FALSE  TRUE 1.92008303 2.29405631 0.41558442
 4: power    TRUE  5    TRUE FALSE 0.00000000 0.00000000 0.45477514
 5: power    TRUE  5    TRUE  TRUE 1.65000000 1.99590583 0.40160643
 6: power    TRUE 10   FALSE FALSE 2.43145370 2.47422680 0.93023256
 7: power    TRUE 10   FALSE  TRUE 5.23076923 4.75195822 1.15243583
 8: power    TRUE 10    TRUE FALSE 0.00000000 0.00000000 1.22762148
 9: power    TRUE 10    TRUE  TRUE 4.11094601 3.57325166 1.12187659
10: typeI   FALSE  5    TRUE FALSE 0.00000000 0.00000000 0.00000000
11: typeI    TRUE  5   FALSE FALSE 0.07037298 0.07047216 0.03428180
12: typeI    TRUE  5   FALSE  TRUE 0.31994312 0.24432810 0.03448276
13: typeI    TRUE  5    TRUE FALSE 0.00000000 0.00000000 0.02049180
14: typeI    TRUE  5    TRUE  TRUE 0.08198401 0.10244852 0.03076923
15: typeI    TRUE 10   FALSE FALSE 0.52930057 0.54012346 0.13869626
16: typeI    TRUE 10   FALSE  TRUE 0.75159714 0.69166363 0.00000000
17: typeI    TRUE 10    TRUE FALSE 0.00000000 0.00000000 0.04098361
18: typeI    TRUE 10    TRUE  TRUE 0.17391304 0.15345269 0.08200923
```

When concluding for efficacy:

```
     hypo missing ar binding  fixC method 1 method 2 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

	method	missing	ar	hypo	fixC	binding	N	pc.all	pc.missing3	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