Adaptive Group Sequential Trials with the Standardized Mean Difference as Effect Size—Results of a Simulation Study

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Abstract: In a thorough and extensive simulation study, we investigate the practical properties of repeated confidence intervals and point estimates for the standardized difference of normal means in adaptive group sequential trials. The theoretical foundations have been described in Hartung and Knapp (2009, 2010). In the simulation study, we consider an adaptive three-stage Pocock (1977)-type design for planning and showing noninferiority and an adaptive five-stage O'Brien-Fleming (1979)-type design for planning and showing superiority.

Keywords: Pocock-type design; O'Brien-Fleming-type design; Noninferiority; Superiority; Repeated confidence intervals

1 Introduction

We consider comparative studies with normally distributed response variables in two independent groups, say experimental E and control C. The parameter of interest is the standardized mean difference, say $\vartheta = (\mu_E - \mu_C)/\sigma$, where μ_E and μ_C denote the means in the two groups and $\sigma^2 > 0$ stands for the common variance of the responses.

Hartung and Knapp (2009, 2010) consider the standardized mean difference in adaptive group sequential trials following the general approach suggested by Hartung (2006). They derive exact and approximate nested repeated confidence intervals for the parameter of interest in each interim analysis based on the knowledge of all previously performed interim analyses. Moreover, they consider point estimates for ϑ in each interim analysis.

In an extensive simulation study, we now investigate the practical properties of the proposed repeated confidence intervals and point estimates for the standardized mean difference, where parts of the results of this simulation study are also reported in Hartung and Knapp (2010).

The present simulation study has several goals: Beside the final nested confidence interval after stopping the sequential trial, one could also use the individual confidence interval from the final analysis. One goal of the simulation study is to determine the actual coverage probabilities of the final nested and the final individual confidence interval as well as their expected lengths. In contrast to the final individual confidence interval, the final nested confidence interval can be empty because of the consecutive intersection of the individual intervals. Theoretically, the probability of obtaining an empty interval is bounded by 2α, where α is the Type I error of the one-sided test problem, see Hartung and Knapp (2009, 2010). In the simulation study, we are interested in the proportions of empty confidence intervals where the possible early stopping of the trial might drastically reduce the number of empty final nested confidence intervals. Beside the exact intervals, where the bounds of the intervals must be determined by solving nonlinear equations, Hartung and Knapp (2009, 2010) propose approximate confidence intervals which are explicitly given. The properties of these intervals, of course, are also of interest and we study these properties independently of the properties of the exact intervals, that is, we conduct separate simulations for the approximate intervals. Finally, Hartung and Knapp (2009, 2010) consider point estimation of the parameter of interest. Theoretically, the exact point estimator is median unbiased. We study here the mean bias and the mean-squared error of the exact point estimator and the approximate point estimator.

The outline of the present paper is as follows: Section 2 contains the results for planning and showing noninferiority in a three-stage adaptive Pocock (1977)-type design. In Section 3, we consider a five-stage adaptive O'Brien-Fleming (1979)-type design for planning and showing superiority.

Throughout the paper the following notations and abbreviations are used in the tables showing the simulation results.

Table 1: Abbrevations and notations used in the paper

Abbreviation or Notation	Explanation
AL	Average length of the confidence interval
ANSt	Average number of performed stages
ASN	Average sample size number
CC	Confidence coefficient (reported in %)
MSE	Mean-squared error
$\emptyset$	Proportion of empty nested confidence intervals (reported in %)
g_0	Prior guess at the onset of the trial
μ_E	True mean in the experimental group (Note: $\mu_C = 0$)
σ^2	True common variance in both groups
ϑ	True standardized mean difference

The simulation study is carried out using the statistic software R, version 2.10.1 (R Development Core Team, 2009). Each parameter estimate is based on 10,000 simulation runs.

2 Planning and Showing Noninferiority

We consider the one-sided significance levels $\alpha = 0.05, 0.025$, and 0.005. An adaptive three-stage Pocock (1977)-type design is considered for showing noninferiority with $\Delta = 0.2$. The critical values are given as follows: $1.992\sqrt{k}$ for $\alpha = 0.05$, $2.289\sqrt{k}$ for $\alpha = 0.025$, and $2.873\sqrt{k}$ for $\alpha = 0.005$, $k = 1, 2, 3$, see Hartung (2006).

The noninferiority margin is always set to $\Delta = 0.2$ and will not be changed during the course of the trial. The trial will be stopped if the lower bound of the exact (or approximate) nested confidence interval CI_k is larger than $-\Delta = -0.2$ the first time. Note that this decision rule is the same for both intervals, the nested and the individual one.

For adaptive sample size planning, we always use a Type II error of $\beta = 0.2$. To avoid large sample sizes near the null hypothesis, we always use the maximum of 0.2 and $\hat{\vartheta} + \Delta$ in the sample size formula, see Hartung and Knapp (2009, 2010), where $\hat{\vartheta}$ denotes the (updated) median unbiased maximum likelihood (ML) estimator.

Without loss of generality, we set $\mu_C = 0$. As means in the experimental group, we consider $\mu_E = -0.2,\ 0,\ 0.2,\ 0.6, 1,$ and 2 and the common variance is chosen as $\sigma^2 = 0.5,\ 1,\ 2$, so that we consider the true standardized mean differences

$$\vartheta = -0.4,\ -0.2,\ -0.1,\ 0,\ 0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.5,\ 0.6,\ 1,\ 1.2,\ 2,\ 4.$$

As prior guesses of ϑ, we consider $g_0 = 0,\ 0.2, 0.5,$ and 0.8. In total, we simulate 72 different trials for each one-sided significance level α.

Tables 2–4 contain the results for the exact confidence intervals given one-sided significance levels of $\alpha = 0.05, 0.025,$ and 0.005. Consequently, the coverage probabilities of the intervals should be at least $100(1 - 2\alpha)\% = 90\%, 95\%,$ and 99%, respectively. Tables 5–7 contain the respective results for the approximate confidence intervals. The (mean) biases and mean-squared errors of the final exact and approximate median unbiased ML estimators are displayed in Table 8 and 9.

The exact intervals always keep the nominal confidence coefficient. In case the adaptive trial passes through all three stages almost surely, the actual confidence coefficient of the nested confidence interval is close to the nominal one. Otherwise the actual confidence coefficient is larger up to roughly $100(1-\alpha)\%$. Based on the construction of the intervals, the actual confidence coefficient of the final individual confidence interval is always larger than the confidence coefficient of the nested interval and mostly close to $100(1-\alpha)\%$. Of course, the final nested confidence interval is always shorter or of equal width than the final individual confidence interval but the difference between the average lengths of the these intervals is practically negligible.

Moreover, it is worthwhile to note that the proportion of empty final nested confidence intervals is of no practical importance. Even for $\alpha = 0.05$, the maximum observed proportion is less than 0.5%.

The approximate intervals also produce very satisfactory results. All the intervals keep the nominal confidence coefficient. The relationship between the nested and the individual interval is nearly the same as for the exact intervals. The actual confidence coefficients of the approximate intervals are slightly smaller compared to the actual confidence coefficients of the exact intervals. The average length of the approximated intervals are comparable to those of the exact intervals. Also, the average number of performed stages and the average sample size number of the trials using the lower bound of the approximate nested confidence interval for stopping the trial are of the same magnitude as those numbers when the lower bound of the exact nested confidence interval is used for stopping the trial.

The results for the point estimates, that is, exact and approximate median unbiased ML estimate, are comparable. The mean-squared error (MSE) of the exact estimator is often smaller than the MSE of the approximate estimator. The most exceptions from this rule occur when the Type I error is $\alpha = 0.05$ and the prior guess is $g_0 = 0.8$, that is, we start the trial with the smallest sample size. With respect to the prior guess, we observe that the absolute value of the (mean) bias and MSE increases when the starting sample size decreases. Moreover, given a parameter set, (mean) bias and MSE of the estimators decreases when the Type I error decreases.

Table 2: Adaptive three-stage Pocock-type trial for **showing noninferiority using exact confidence intervals** and one-sided significance level of $\alpha = 0.05$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0	-0.2	0.5	-0.4	90.50	0.18	0.03	95.51	0.19	3	1044
0.2	-0.2	0.5	-0.4	90.88	0.23	0.05	95.90	0.24	3	836
0.5	-0.2	0.5	-0.4	90.64	0.29	0.09	95.29	0.30	2.98	718
0.8	-0.2	0.5	-0.4	91.65	0.34	0.02	95.62	0.36	2.99	653
0	-0.2	1	-0.2	89.85	0.19	0.02	92.41	0.20	2.93	1027
0.2	-0.2	1	-0.2	89.91	0.24	0.09	92.69	0.25	2.94	870
0.5	-0.2	1	-0.2	91.41	0.30	0.10	93.59	0.31	2.95	762
0.8	-0.2	1	-0.2	91.50	0.37	0.11	93.49	0.38	2.95	690
0	-0.2	2	-0.1	92.25	0.26	0.03	94.48	0.27	2.62	644
0.2	-0.2	2	-0.1	91.85	0.31	0.16	94.28	0.32	2.80	634
0.5	-0.2	2	-0.1	92.25	0.37	0.18	94.29	0.38	2.87	603
0.8	-0.2	2	-0.1	92.84	0.42	0.25	94.93	0.43	2.91	572
0	0	0.5	0	93.14	0.35	0.02	95.62	0.36	1.97	330
0.2	0	0.5	0	92.41	0.42	0.19	94.81	0.43	2.47	373
0.5	0	0.5	0	92.09	0.48	0.24	94.62	0.49	2.68	411
0.8	0	0.5	0	93.11	0.53	0.21	95.11	0.54	2.75	413
0	0	1	0	92.57	0.35	0.07	95.01	0.36	1.96	329
0.2	0	1	0	92.56	0.42	0.25	94.84	0.43	2.47	375
0.5	0	1	0	92.46	0.48	0.27	94.82	0.49	2.68	406
0.8	0	1	0	93.07	0.53	0.16	95.28	0.54	2.76	409
0	0	2	0	93.21	0.35	0.02	95.69	0.36	1.97	329
0.2	0	2	0	92.31	0.42	0.25	95.03	0.43	2.46	370
0.5	0	2	0	92.58	0.48	0.22	95.06	0.49	2.67	409
0.8	0	2	0	92.76	0.54	0.27	94.83	0.55	2.75	407
0	0.2	0.5	0.4	95.12	0.49	0	95.15	0.49	1	134
0.2	0.2	0.5	0.4	93.59	0.84	0.01	95.39	0.86	1.36	62
0.5	0.2	0.5	0.4	93.86	1.00	0.16	95.62	1.02	1.91	92
0.8	0.2	0.5	0.4	94.00	1.06	0.46	95.88	1.08	2.17	113
0	0.2	1	0.2	94.48	0.47	0	96.03	0.48	1.1	146
0.2	0.2	1	0.2	93.86	0.67	0.09	95.75	0.68	1.77	130
0.5	0.2	1	0.2	93.16	0.75	0.42	95.62	0.76	2.17	172
0.8	0.2	1	0.2	93.53	0.78	0.43	95.85	0.79	2.39	203
0	0.2	2	0.1	93.31	0.43	0.03	95.87	0.44	1.38	190
0.2	0.2	2	0.1	92.80	0.55	0.22	95.55	0.56	2.06	209
0.5	0.2	2	0.1	92.71	0.62	0.36	95.09	0.63	2.39	253

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.8	0.2	2	0.1	93.42	0.66	0.25	95.50	0.68	2.53	281
0	0.6	0.5	1.2	95.52	0.53	0	95.52	0.53	1	134
0.2	0.6	0.5	1.2	95.54	1.05	0	95.54	1.05	1	34
0.5	0.6	0.5	1.2	94.96	1.73	0.11	96.57	1.75	1.1	14
0.8	0.6	0.5	1.2	94.39	2.14	0.11	96.09	2.18	1.5	18
0	0.6	1	0.6	95.41	0.50	0	95.41	0.50	1	134
0.2	0.6	1	0.6	94.58	0.95	0.04	96.53	0.96	1.1	40
0.5	0.6	1	0.6	94.23	1.25	0.08	95.83	1.27	1.64	50
0.8	0.6	1	0.6	94.66	1.34	0.33	96.11	1.36	2	73
0	0.6	2	0.3	95.56	0.49	0	96.86	0.49	1.02	136
0.2	0.6	2	0.3	93.70	0.77	0.02	95.61	0.78	1.55	87
0.5	0.6	2	0.3	93.62	0.87	0.44	95.67	0.88	2.04	126
0.8	0.6	2	0.3	94.17	0.92	0.50	96.25	0.93	2.27	152
0	1	0.5	2	95.16	0.60	0	95.16	0.60	1	134
0.2	1	0.5	2	95.47	1.19	0	95.47	1.19	1	34
0.5	1	0.5	2	95.60	2.03	0	95.63	2.03	1	12
0.8	1	0.5	2	94.29	2.87	0.01	96.12	2.89	1.09	7
0	1	1	1	95.51	0.52	0	95.51	0.52	1	134
0.2	1	1	1	95.58	1.03	0	95.66	1.03	1	34
0.5	1	1	1	94.28	1.62	0.11	96.26	1.64	1.22	18
0.8	1	1	1	94.51	1.89	0.10	96.44	1.93	1.66	29
0	1	2	0.5	95.25	0.49	0	95.27	0.49	1	134
0.2	1	2	0.5	94.71	0.91	0.04	96.47	0.92	1.20	47
0.5	1	2	0.5	93.95	1.13	0.13	95.72	1.15	1.77	69
0.8	1	2	0.5	94.63	1.20	0.41	96.11	1.22	2.10	91
0	2	0.5	4	95.28	0.84	0	95.28	0.84	1	134
0.2	2	0.5	4	95.23	1.69	0	95.23	1.69	1	34
0.5	2	0.5	4	94.67	2.90	0	94.67	2.90	1	12
0.8	2	0.5	4	94.05	4.23	0	94.05	4.23	1	6
0	2	1	2	95.67	0.60	0	95.67	0.60	1	134
0.2	2	1	2	95.77	1.19	0	95.77	1.19	1	34
0.5	2	1	2	95.40	2.03	0	95.42	2.03	1	12
0.8	2	1	2	94.20	2.87	0.03	96.38	2.89	1.09	7
0	2	2	1	95.32	0.52	0	95.32	0.52	1	134
0.2	2	2	1	95.38	1.03	0	95.47	1.03	1	34
0.5	2	2	1	94.09	1.62	0.25	96.17	1.64	1.22	18
0.8	2	2	1	93.81	1.90	0.03	95.53	1.93	1.67	29

Table 3: Adaptive three-stage Pocock-type trial for **showing noninferiority using exact confidence intervals** and one-sided significance level of $\alpha = 0.025$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0	-0.2	0.5	-0.4	94.86	0.20	0	97.65	0.21	3	1095
0.2	-0.2	0.5	-0.4	95.84	0.25	0.01	98.16	0.26	3	890
0.5	-0.2	0.5	-0.4	95.55	0.31	0.01	97.92	0.32	3	775
0.8	-0.2	0.5	-0.4	96.08	0.36	0	97.87	0.37	2.99	718
0	-0.2	1	-0.2	94.98	0.20	0	96.49	0.20	2.97	1163
0.2	-0.2	1	-0.2	94.95	0.25	0	96.40	0.25	2.97	984
0.5	-0.2	1	-0.2	95.58	0.31	0	96.69	0.31	2.97	862
0.8	-0.2	1	-0.2	95.67	0.35	0	96.77	0.36	2.97	797
0	-0.2	2	-0.1	95.94	0.26	0	97.38	0.26	2.73	796
0.2	-0.2	2	-0.1	96.10	0.30	0.01	97.26	0.31	2.88	764
0.5	-0.2	2	-0.1	96.19	0.36	0.02	97.43	0.37	2.93	716
0.8	-0.2	2	-0.1	96.31	0.40	0.01	97.40	0.41	2.95	682
0	0	0.5	0	96.24	0.36	0	97.63	0.37	2.04	404
0.2	0	0.5	0	96.36	0.42	0.04	97.58	0.42	2.57	454
0.5	0	0.5	0	96.39	0.47	0.06	97.74	0.48	2.76	486
0.8	0	0.5	0	96.27	0.51	0.02	97.41	0.51	2.82	486
0	0	1	0	96.69	0.36	0.02	97.98	0.37	2.03	398
0.2	0	1	0	95.98	0.42	0.03	97.20	0.43	2.57	452
0.5	0	1	0	96.16	0.47	0.04	97.43	0.48	2.76	479
0.8	0	1	0	96.12	0.51	0.05	97.25	0.51	2.81	486
0	0	2	0	96.52	0.36	0	97.84	0.37	2.04	404
0.2	0	2	0	96.29	0.42	0.03	97.78	0.42	2.57	454
0.5	0	2	0	96.36	0.46	0.05	97.57	0.47	2.76	488
0.8	0	2	0	96.57	0.50	0.02	97.42	0.51	2.81	492
0	0.2	0.5	0.4	97.72	0.51	0	97.75	0.51	1	164
0.2	0.2	0.5	0.4	97.04	0.89	0	97.95	0.90	1.37	70
0.5	0.2	0.5	0.4	97.30	1.04	0.10	98.14	1.05	2.01	105
0.8	0.2	0.5	0.4	97.18	1.06	0.11	98.08	1.07	2.22	129
0	0.2	1	0.2	97.40	0.49	0	98.41	0.50	1.10	176
0.2	0.2	1	0.2	96.99	0.69	0.05	98.07	0.69	1.84	154
0.5	0.2	1	0.2	97.12	0.75	0.04	98.32	0.76	2.27	198
0.8	0.2	1	0.2	97.03	0.77	0.13	98.18	0.78	2.41	227
0	0.2	2	0.1	96.68	0.45	0	98.10	0.46	1.40	228
0.2	0.2	2	0.1	96.64	0.56	0.03	97.89	0.56	2.14	252
0.5	0.2	2	0.1	96.24	0.61	0.08	97.50	0.61	2.46	302
0.8	0.2	2	0.1	96.86	0.63	0.04	97.92	0.64	2.59	326
0	0.6	0.5	1.2	97.96	0.55	0	97.96	0.55	1	164
0.2	0.6	0.5	1.2	97.78	1.09	0	97.78	1.09	1	42

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.5	0.6	0.5	1.2	96.99	1.84	0.01	98.20	1.86	1.11	16
0.8	0.6	0.5	1.2	96.85	2.17	0.05	97.91	2.21	1.48	18
0	0.6	1	0.6	97.76	0.52	0	97.76	0.52	1	164
0.2	0.6	1	0.6	97.13	0.99	0	98.09	1.00	1.10	47
0.5	0.6	1	0.6	97.15	1.31	0.02	97.88	1.33	1.73	56
0.8	0.6	1	0.6	97.20	1.36	0.08	97.94	1.37	2.05	78
0	0.6	2	0.3	97.74	0.51	0	98.66	0.51	1.01	166
0.2	0.6	2	0.3	97.00	0.80	0	97.96	0.81	1.59	101
0.5	0.6	2	0.3	97.14	0.90	0.14	98.05	0.91	2.13	142
0.8	0.6	2	0.3	97.42	0.91	0.10	98.39	0.91	2.32	171
0	1	0.5	2	97.79	0.62	0	97.79	0.62	1	164
0.2	1	0.5	2	97.46	1.23	0	97.46	1.23	1	42
0.5	1	0.5	2	98.20	2.16	0	98.23	2.16	1	14
0.8	1	0.5	2	97.32	2.86	0	98.44	2.87	1.05	8
0	1	1	1	97.77	0.54	0	97.77	0.54	1	164
0.2	1	1	1	97.61	1.06	0	97.67	1.06	1	42
0.5	1	1	1	97.14	1.72	0.03	98.23	1.74	1.25	20
0.8	1	1	1	96.96	1.95	0.02	97.83	1.98	1.65	28
0	1	2	0.5	97.68	0.51	0	97.68	0.51	1	164
0.2	1	2	0.5	97.07	0.95	0	98.11	0.96	1.19	54
0.5	1	2	0.5	97.11	1.17	0.01	98.06	1.18	1.88	78
0.8	1	2	0.5	97.48	1.21	0.08	98.26	1.22	2.14	101
0	2	0.5	4	97.97	0.88	0	97.97	0.88	1	164
0.2	2	0.5	4	97.71	1.74	0	97.71	1.74	1	42
0.5	2	0.5	4	97.59	3.07	0	97.59	3.07	1	14
0.8	2	0.5	4	97.20	4.14	0	97.20	4.14	1	8
0	2	1	2	97.95	0.62	0	97.95	0.62	1	164
0.2	2	1	2	97.83	1.23	0	97.83	1.23	1	42
0.5	2	1	2	97.86	2.15	0	97.88	2.15	1	14
0.8	2	1	2	97.56	2.86	0.02	98.56	2.87	1.04	8
0	2	2	1	98.02	0.54	0	98.02	0.54	1	164
0.2	2	2	1	97.65	1.06	0	97.68	1.06	1	42
0.5	2	2	1	97.15	1.72	0.01	98.26	1.74	1.25	20
0.8	2	2	1	97.03	1.95	0	97.84	1.97	1.65	28

Table 4: Adaptive three-stage Pocock-type trial for **showing noninferiority using exact confidence intervals** and one-sided significance level of $\alpha = 0.005$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0	-0.2	0.5	-0.4	99.32	0.25	0	99.74	0.25	3	1176
0.2	-0.2	0.5	-0.4	98.97	0.31	0	99.52	0.31	3	938
0.5	-0.2	0.5	-0.4	98.99	0.37	0	99.54	0.37	3	834
0.8	-0.2	0.5	-0.4	99.12	0.42	0	99.55	0.42	3	771
0	-0.2	1	-0.2	99.17	0.23	0	99.48	0.23	3	1344
0.2	-0.2	1	-0.2	98.86	0.27	0	99.19	0.28	2.99	1124
0.5	-0.2	1	-0.2	99.12	0.33	0	99.38	0.33	3	981
0.8	-0.2	1	-0.2	99.28	0.37	0	99.46	0.38	3	896
0	-0.2	2	-0.1	99.16	0.27	0	99.48	0.27	2.86	1053
0.2	-0.2	2	-0.1	99.05	0.31	0	99.38	0.31	2.96	976
0.5	-0.2	2	-0.1	99.33	0.36	0	99.51	0.36	2.98	893
0.8	-0.2	2	-0.1	99.33	0.40	0	99.61	0.41	2.99	828
0	0	0.5	0	99.26	0.38	0	99.64	0.38	2.22	569
0.2	0	0.5	0	99.25	0.41	0	99.53	0.42	2.75	627
0.5	0	0.5	0	99.31	0.46	0	99.55	0.46	2.88	641
0.8	0	0.5	0	99.31	0.49	0	99.56	0.50	2.93	627
0	0	1	0	99.46	0.38	0	99.68	0.38	2.22	573
0.2	0	1	0	99.31	0.41	0	99.57	0.41	2.75	630
0.5	0	1	0	99.32	0.45	0	99.59	0.45	2.89	648
0.8	0	1	0	99.25	0.48	0	99.53	0.49	2.93	642
0	0	2	0	99.29	0.38	0	99.58	0.38	2.22	572
0.2	0	2	0	99.25	0.41	0	99.54	0.42	2.75	630
0.5	0	2	0	99.25	0.46	0	99.62	0.46	2.88	645
0.8	0	2	0	99.30	0.49	0	99.52	0.49	2.93	637
0	0.2	0.5	0.4	99.63	0.55	0	99.65	0.55	1	226
0.2	0.2	0.5	0.4	99.47	0.96	0	99.69	0.97	1.43	88
0.5	0.2	0.5	0.4	99.49	1.06	0.01	99.68	1.06	2.18	130
0.8	0.2	0.5	0.4	99.43	1.06	0	99.64	1.07	2.38	157
0	0.2	1	0.2	99.44	0.53	0	99.67	0.53	1.09	239
0.2	0.2	1	0.2	99.36	0.71	0	99.69	0.72	2.02	204
0.5	0.2	1	0.2	99.16	0.75	0.01	99.52	0.76	2.41	250
0.8	0.2	1	0.2	99.51	0.76	0	99.73	0.77	2.55	274
0	0.2	2	0.1	99.27	0.48	0	99.61	0.49	1.45	314
0.2	0.2	2	0.1	99.30	0.56	0	99.64	0.56	2.35	349
0.5	0.2	2	0.1	99.40	0.59	0.01	99.57	0.60	2.63	388
0.8	0.2	2	0.1	99.32	0.62	0	99.52	0.63	2.73	412
0	0.6	0.5	1.2	99.69	0.59	0	99.69	0.59	1	226
0.2	0.6	0.5	1.2	99.54	1.17	0	99.54	1.17	1	57

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.5	0.6	0.5	1.2	99.42	1.99	0	99.62	2.01	1.11	21
0.8	0.6	0.5	1.2	99.52	2.38	0	99.69	2.41	1.64	21
0	0.6	1	0.6	99.54	0.55	0	99.54	0.55	1	226
0.2	0.6	1	0.6	99.37	1.08	0	99.56	1.08	1.09	61
0.5	0.6	1	0.6	99.34	1.39	0	99.54	1.40	1.88	65
0.8	0.6	1	0.6	99.51	1.41	0	99.66	1.41	2.26	89
0	0.6	2	0.3	99.56	0.54	0	99.71	0.54	1.01	227
0.2	0.6	2	0.3	99.40	0.85	0.01	99.64	0.86	1.72	131
0.5	0.6	2	0.3	99.46	0.90	0	99.68	0.90	2.31	177
0.8	0.6	2	0.3	99.47	0.91	0	99.70	0.92	2.46	204
0	1	0.5	2	99.60	0.66	0	99.60	0.66	1	226
0.2	1	0.5	2	99.59	1.32	0	99.59	1.32	1	57
0.5	1	0.5	2	99.61	2.31	0	99.62	2.31	1	19
0.8	1	0.5	2	99.39	3.18	0	99.66	3.20	1.07	10
0	1	1	1	99.60	0.57	0	99.60	0.57	1	226
0.2	1	1	1	99.61	1.14	0	99.63	1.14	1	57
0.5	1	1	1	99.33	1.86	0	99.62	1.88	1.28	25
0.8	1	1	1	99.46	2.08	0.01	99.63	2.10	1.87	33
0	1	2	0.5	99.53	0.55	0	99.53	0.55	1	226
0.2	1	2	0.5	99.35	1.03	0	99.59	1.04	1.23	70
0.5	1	2	0.5	99.48	1.23	0	99.62	1.24	2.04	91
0.8	1	2	0.5	99.40	1.22	0	99.66	1.23	2.33	120
0	2	0.5	4	99.60	0.94	0	99.60	0.94	1	226
0.2	2	0.5	4	99.56	1.88	0	99.56	1.88	1	57
0.5	2	0.5	4	99.44	3.28	0	99.44	3.28	1	19
0.8	2	0.5	4	99.49	4.60	0	99.49	4.60	1	10
0	2	1	2	99.61	0.66	0	99.61	0.66	1	226
0.2	2	1	2	99.62	1.32	0	99.62	1.32	1	57
0.5	2	1	2	99.57	2.31	0	99.59	2.31	1	19
0.8	2	1	2	99.29	3.18	0	99.58	3.20	1.07	10
0	2	2	1	99.58	0.57	0	99.58	0.57	1	226
0.2	2	2	1	99.60	1.15	0	99.61	1.15	1	57
0.5	2	2	1	99.43	1.85	0	99.59	1.87	1.30	25
0.8	2	2	1	99.41	2.08	0	99.62	2.10	1.86	32

Table 5: Adaptive three-stage Pocock-type trial for **showing noninferiority using approximate confidence intervals** and one-sided significance level of $\alpha = 0.05$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0	-0.2	0.5	-0.4	89.81	0.18	0.04	95.24	0.19	3	1040
0.2	-0.2	0.5	-0.4	90.27	0.23	0.07	95.18	0.24	2.99	831
0.5	-0.2	0.5	-0.4	90.23	0.29	0.11	94.95	0.31	2.99	710
0.8	-0.2	0.5	-0.4	91.29	0.36	0.03	95.08	0.37	2.98	643
0	-0.2	1	-0.2	90.20	0.19	0.06	92.85	0.20	2.94	1036
0.2	-0.2	1	-0.2	90.03	0.24	0.11	92.64	0.25	2.94	871
0.5	-0.2	1	-0.2	90.33	0.31	0.14	92.95	0.32	2.94	756
0.8	-0.2	1	-0.2	92.21	0.36	0.11	94.25	0.38	2.96	685
0	-0.2	2	-0.1	92.23	0.26	0.01	94.70	0.27	2.62	649
0.2	-0.2	2	-0.1	91.34	0.31	0.18	93.95	0.32	2.79	639
0.5	-0.2	2	-0.1	91.66	0.37	0.15	94.16	0.38	2.87	604
0.8	-0.2	2	-0.1	92.60	0.43	0.12	94.57	0.45	2.90	567
0	0	0.5	0	92.92	0.35	0.06	95.70	0.36	1.96	326
0.2	0	0.5	0	92.29	0.42	0.21	94.95	0.43	2.47	374
0.5	0	0.5	0	92.24	0.48	0.17	94.73	0.49	2.66	402
0.8	0	0.5	0	92.54	0.54	0.22	94.67	0.56	2.75	406
0	0	1	0	93.13	0.35	0.05	95.53	0.36	1.94	324
0.2	0	1	0	92.31	0.42	0.19	94.80	0.43	2.47	372
0.5	0	1	0	92.62	0.48	0.30	95.09	0.49	2.67	403
0.8	0	1	0	92.60	0.54	0.12	94.71	0.55	2.76	410
0	0	2	0	92.42	0.35	0.05	95.35	0.36	1.96	331
0.2	0	2	0	92.22	0.42	0.17	94.83	0.43	2.47	375
0.5	0	2	0	92.44	0.48	0.28	94.83	0.49	2.67	405
0.8	0	2	0	92.95	0.54	0.19	94.87	0.55	2.76	411
0	0.2	0.5	0.4	95.13	0.49	0	95.19	0.49	1	134
0.2	0.2	0.5	0.4	93.57	0.85	0.05	95.67	0.86	1.34	62
0.5	0.2	0.5	0.4	94.06	1.01	0.24	95.87	1.03	1.90	92
0.8	0.2	0.5	0.4	94.70	1.08	0.49	96.62	1.10	2.17	114
0	0.2	1	0.2	94.53	0.47	0	96.25	0.48	1.10	146
0.2	0.2	1	0.2	93.32	0.66	0.13	95.67	0.67	1.79	132
0.5	0.2	1	0.2	93.51	0.75	0.37	95.84	0.76	2.18	171
0.8	0.2	1	0.2	93.82	0.81	0.36	95.94	0.82	2.37	198
0	0.2	2	0.1	93.88	0.43	0.01	96.37	0.44	1.36	187
0.2	0.2	2	0.1	92.84	0.55	0.21	95.55	0.56	2.07	209
0.5	0.2	2	0.1	92.65	0.61	0.39	95.29	0.62	2.39	255
0.8	0.2	2	0.1	93.14	0.67	0.18	95.53	0.68	2.55	283
0	0.6	0.5	1.2	95.57	0.53	0	95.57	0.53	1	134

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.2	0.6	0.5	1.2	96.04	1.06	0	96.04	1.06	1	34
0.5	0.6	0.5	1.2	95.12	1.75	0.08	96.68	1.77	1.09	14
0.8	0.6	0.5	1.2	94.20	2.20	0.18	96.43	2.24	1.50	19
0	0.6	1	0.6	95.35	0.50	0	95.35	0.50	1	134
0.2	0.6	1	0.6	94.88	0.96	0.01	96.58	0.97	1.10	39
0.5	0.6	1	0.6	93.98	1.27	0.09	95.77	1.29	1.62	49
0.8	0.6	1	0.6	94.67	1.37	0.30	96.40	1.39	2.01	71
0	0.6	2	0.3	95.14	0.49	0.01	96.33	0.49	1.02	136
0.2	0.6	2	0.3	93.70	0.77	0.03	95.33	0.78	1.54	86
0.5	0.6	2	0.3	93.81	0.88	0.38	95.76	0.89	2.03	124
0.8	0.6	2	0.3	94.43	0.93	0.49	96.60	0.94	2.28	149
0	1	0.5	2	95.50	0.60	0	95.50	0.60	1	134
0.2	1	0.5	2	95.44	1.20	0	95.44	1.20	1	34
0.5	1	0.5	2	95.71	2.06	0	95.72	2.06	1	12
0.8	1	0.5	2	95.52	2.97	0.06	97.23	3.00	1.09	7
0	1	1	1	95.15	0.52	0	95.15	0.52	1	134
0.2	1	1	1	95.65	1.03	0	95.72	1.03	1	34
0.5	1	1	1	94.40	1.63	0.11	96.42	1.66	1.21	18
0.8	1	1	1	95.03	1.96	0.04	96.58	1.99	1.65	27
0	1	2	0.5	95.39	0.49	0	95.39	0.49	1	134
0.2	1	2	0.5	94.15	0.91	0.03	95.95	0.92	1.21	47
0.5	1	2	0.5	94.14	1.14	0.11	95.86	1.16	1.77	67
0.8	1	2	0.5	94.69	1.23	0.39	96.48	1.25	2.09	89
0	2	0.5	4	95.49	0.85	0	95.49	0.85	1	134
0.2	2	0.5	4	95.39	1.70	0	95.39	1.70	1	34
0.5	2	0.5	4	95.37	2.98	0	95.37	2.98	1	12
0.8	2	0.5	4	95.76	4.54	0	95.76	4.54	1	6
0	2	1	2	95.22	0.60	0	95.22	0.60	1	134
0.2	2	1	2	95.69	1.20	0	95.69	1.20	1	34
0.5	2	1	2	95.68	2.06	0	95.71	2.06	1	12
0.8	2	1	2	95.30	2.99	0.06	97.41	3.01	1.09	7
0	2	2	1	95.37	0.52	0	95.37	0.52	1	134
0.2	2	2	1	95.40	1.03	0	95.48	1.03	1	34
0.5	2	2	1	94.90	1.63	0.15	96.67	1.66	1.21	18
0.8	2	2	1	94.52	1.94	0.04	96.36	1.98	1.66	29

Table 6: Adaptive three-stage Pocock-type trial for **showing noninferiority using approximate confidence intervals** and one-sided significance level of $\alpha = 0.025$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0	-0.2	0.5	-0.4	95.23	0.20	0	97.93	0.21	3	1093
0.2	-0.2	0.5	-0.4	95.28	0.26	0.01	97.90	0.26	3	885
0.5	-0.2	0.5	-0.4	95.10	0.32	0.03	97.89	0.33	3	768
0.8	-0.2	0.5	-0.4	95.75	0.36	0	97.72	0.37	2.99	708
0	-0.2	1	-0.2	95.13	0.20	0.01	96.55	0.20	2.97	1166
0.2	-0.2	1	-0.2	95.36	0.24	0	96.72	0.25	2.97	990
0.5	-0.2	1	-0.2	94.93	0.31	0.04	96.44	0.32	2.97	855
0.8	-0.2	1	-0.2	96.09	0.35	0.02	97.34	0.36	2.98	790
0	-0.2	2	-0.1	96.09	0.26	0.01	97.27	0.27	2.72	786
0.2	-0.2	2	-0.1	95.56	0.30	0.03	97.10	0.31	2.88	767
0.5	-0.2	2	-0.1	96.06	0.36	0.01	97.23	0.37	2.92	714
0.8	-0.2	2	-0.1	96.54	0.40	0.05	97.73	0.41	2.94	677
0	0	0.5	0	96.49	0.36	0	97.89	0.37	2.04	401
0.2	0	0.5	0	96.42	0.42	0.02	97.65	0.43	2.57	455
0.5	0	0.5	0	96.29	0.47	0.04	97.59	0.48	2.75	482
0.8	0	0.5	0	96.21	0.51	0.02	97.42	0.52	2.81	485
0	0	1	0	96.51	0.36	0.01	97.88	0.37	2.03	400
0.2	0	1	0	96.24	0.42	0.04	97.57	0.42	2.58	453
0.5	0	1	0	96.49	0.47	0.07	97.59	0.47	2.76	483
0.8	0	1	0	96.11	0.51	0.05	97.33	0.52	2.82	490
0	0	2	0	96.34	0.36	0.01	97.82	0.37	2.04	403
0.2	0	2	0	96.19	0.42	0.06	97.60	0.42	2.57	452
0.5	0	2	0	96.18	0.47	0.05	97.45	0.47	2.76	487
0.8	0	2	0	96.40	0.50	0.04	97.52	0.51	2.82	491
0	0.2	0.5	0.4	97.53	0.51	0	97.58	0.51	1	164
0.2	0.2	0.5	0.4	97.03	0.89	0	98.03	0.90	1.36	70
0.5	0.2	0.5	0.4	97.27	1.05	0.10	98.05	1.06	1.99	106
0.8	0.2	0.5	0.4	97.23	1.06	0.13	98.31	1.07	2.23	129
0	0.2	1	0.2	97.12	0.49	0	98.19	0.50	1.1	176
0.2	0.2	1	0.2	96.62	0.69	0.02	97.68	0.69	1.84	154
0.5	0.2	1	0.2	96.95	0.75	0.1	98.29	0.76	2.27	203
0.8	0.2	1	0.2	97.00	0.79	0.07	98.09	0.80	2.41	223
0	0.2	2	0.1	96.83	0.45	0	98.21	0.46	1.39	226
0.2	0.2	2	0.1	96.34	0.56	0.04	97.90	0.57	2.14	249
0.5	0.2	2	0.1	96.39	0.61	0.06	97.69	0.62	2.47	307
0.8	0.2	2	0.1	97.02	0.63	0.05	98.03	0.64	2.58	323
0	0.6	0.5	1.2	97.84	0.55	0	97.84	0.55	1	164

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.2	0.6	0.5	1.2	97.92	1.09	0	97.92	1.09	1	42
0.5	0.6	0.5	1.2	97.24	1.85	0.02	98.35	1.87	1.11	16
0.8	0.6	0.5	1.2	97.47	2.23	0.02	98.38	2.27	1.46	17
0	0.6	1	0.6	97.82	0.52	0	97.82	0.52	1	164
0.2	0.6	1	0.6	97.41	0.99	0	98.33	1.00	1.09	46
0.5	0.6	1	0.6	97.25	1.32	0.02	98.15	1.34	1.72	56
0.8	0.6	1	0.6	97.36	1.39	0.09	98.20	1.40	2.05	76
0	0.6	2	0.3	97.70	0.51	0	98.50	0.51	1.01	165
0.2	0.6	2	0.3	96.72	0.80	0	97.62	0.81	1.59	100
0.5	0.6	2	0.3	97.21	0.90	0.08	98.16	0.90	2.14	142
0.8	0.6	2	0.3	97.21	0.92	0.11	98.19	0.93	2.31	169
0	1	0.5	2	97.85	0.62	0	97.85	0.62	1	164
0.2	1	0.5	2	98.15	1.23	0	98.15	1.23	1	42
0.5	1	0.5	2	98.07	2.18	0	98.10	2.18	1	14
0.8	1	0.5	2	97.82	2.93	0	98.72	2.95	1.05	8
0	1	1	1	97.81	0.54	0	97.81	0.54	1	164
0.2	1	1	1	98.09	1.07	0	98.10	1.07	1	42
0.5	1	1	1	96.97	1.73	0.03	98.12	1.75	1.24	21
0.8	1	1	1	97.33	1.98	0.02	98.25	2.01	1.65	27
0	1	2	0.5	98.04	0.51	0	98.04	0.51	1	164
0.2	1	2	0.5	97.08	0.95	0	98.00	0.96	1.2	54
0.5	1	2	0.5	96.97	1.18	0.06	98.05	1.19	1.88	77
0.8	1	2	0.5	97.28	1.22	0.18	98.12	1.23	2.14	100
0	2	0.5	4	97.56	0.88	0	97.56	0.88	1	164
0.2	2	0.5	4	97.58	1.76	0	97.58	1.76	1	42
0.5	2	0.5	4	97.93	3.15	0	97.93	3.15	1	14
0.8	2	0.5	4	98.14	4.34	0	98.14	4.34	1	8
0	2	1	2	97.56	0.62	0	97.56	0.62	1	164
0.2	2	1	2	97.87	1.23	0	97.87	1.23	1	42
0.5	2	1	2	98.04	2.19	0	98.07	2.19	1	14
0.8	2	1	2	97.69	2.93	0	98.70	2.94	1.04	8
0	2	2	1	97.83	0.54	0	97.83	0.54	1	164
0.2	2	2	1	97.76	1.07	0	97.78	1.07	1	42
0.5	2	2	1	96.99	1.73	0.01	98.17	1.75	1.24	20
0.8	2	2	1	97.13	1.98	0.01	98.05	2.01	1.65	28

Table 7: Adaptive three-stage Pocock-type trial for **showing noninferiority using approximate confidence intervals** and one-sided significance level of $\alpha = 0.005$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0	-0.2	0.5	-0.4	99.27	0.25	0	99.72	0.25	3	1175
0.2	-0.2	0.5	-0.4	98.92	0.31	0	99.48	0.31	3	936
0.5	-0.2	0.5	-0.4	98.98	0.37	0	99.52	0.37	3	830
0.8	-0.2	0.5	-0.4	99.07	0.42	0	99.53	0.43	3	765
0	-0.2	1	-0.2	99.16	0.23	0	99.48	0.23	3	1344
0.2	-0.2	1	-0.2	98.84	0.27	0	99.19	0.28	2.99	1124
0.5	-0.2	1	-0.2	99.09	0.33	0	99.36	0.33	3	979
0.8	-0.2	1	-0.2	99.26	0.38	0	99.44	0.38	3	892
0	-0.2	2	-0.1	99.16	0.27	0	99.48	0.27	2.86	1053
0.2	-0.2	2	-0.1	99.04	0.31	0	99.38	0.31	2.96	976
0.5	-0.2	2	-0.1	99.29	0.36	0	99.48	0.36	2.98	891
0.8	-0.2	2	-0.1	99.34	0.40	0	99.62	0.41	2.99	825
0	0	0.5	0	99.26	0.38	0	99.64	0.38	2.22	569
0.2	0	0.5	0	99.24	0.41	0	99.52	0.42	2.75	627
0.5	0	0.5	0	99.30	0.46	0	99.55	0.46	2.88	641
0.8	0	0.5	0	99.30	0.50	0	99.54	0.50	2.93	624
0	0	1	0	99.45	0.38	0	99.67	0.38	2.22	573
0.2	0	1	0	99.30	0.41	0	99.56	0.42	2.75	630
0.5	0	1	0	99.30	0.45	0	99.59	0.45	2.89	648
0.8	0	1	0	99.28	0.49	0	99.54	0.49	2.93	641
0	0	2	0	99.29	0.38	0	99.58	0.38	2.22	572
0.2	0	2	0	99.25	0.41	0	99.54	0.42	2.75	630
0.5	0	2	0	99.27	0.46	0	99.63	0.46	2.88	644
0.8	0	2	0	99.27	0.49	0	99.49	0.50	2.93	635
0	0.2	0.5	0.4	99.63	0.55	0	99.65	0.55	1	226
0.2	0.2	0.5	0.4	99.47	0.96	0	99.69	0.97	1.43	88
0.5	0.2	0.5	0.4	99.52	1.06	0.01	99.72	1.07	2.18	129
0.8	0.2	0.5	0.4	99.47	1.07	0	99.68	1.08	2.38	157
0	0.2	1	0.2	99.44	0.53	0	99.67	0.53	1.09	239
0.2	0.2	1	0.2	99.35	0.72	0	99.68	0.72	2.02	203
0.5	0.2	1	0.2	99.17	0.76	0.01	99.52	0.76	2.41	250
0.8	0.2	1	0.2	99.49	0.77	0	99.72	0.77	2.56	274
0	0.2	2	0.1	99.27	0.48	0	99.61	0.49	1.45	314
0.2	0.2	2	0.1	99.28	0.56	0	99.63	0.56	2.35	349
0.5	0.2	2	0.1	99.38	0.60	0.01	99.55	0.60	2.63	388
0.8	0.2	2	0.1	99.29	0.63	0	99.49	0.63	2.73	411
0	0.6	0.5	1.2	99.69	0.59	0	99.69	0.59	1	226

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.2	0.6	0.5	1.2	99.54	1.17	0	99.54	1.17	1	57
0.5	0.6	0.5	1.2	99.46	2.00	0	99.67	2.02	1.11	21
0.8	0.6	0.5	1.2	99.55	2.41	0	99.73	2.45	1.65	21
0	0.6	1	0.6	99.53	0.55	0	99.53	0.55	1	226
0.2	0.6	1	0.6	99.36	1.08	0	99.55	1.08	1.09	61
0.5	0.6	1	0.6	99.35	1.40	0	99.56	1.41	1.88	65
0.8	0.6	1	0.6	99.55	1.42	0.01	99.71	1.43	2.26	89
0	0.6	2	0.3	99.56	0.54	0	99.71	0.54	1.01	227
0.2	0.6	2	0.3	99.40	0.85	0.01	99.64	0.86	1.72	130
0.5	0.6	2	0.3	99.45	0.90	0	99.69	0.91	2.31	177
0.8	0.6	2	0.3	99.52	0.92	0	99.74	0.92	2.46	203
0	1	0.5	2	99.60	0.66	0	99.60	0.66	1	226
0.2	1	0.5	2	99.60	1.33	0	99.60	1.33	1	57
0.5	1	0.5	2	99.65	2.33	0	99.66	2.33	1	19
0.8	1	0.5	2	99.48	3.24	0	99.76	3.26	1.07	10
0	1	1	1	99.61	0.57	0	99.61	0.57	1	226
0.2	1	1	1	99.61	1.15	0	99.63	1.15	1	57
0.5	1	1	1	99.35	1.87	0	99.63	1.89	1.28	25
0.8	1	1	1	99.51	2.11	0.01	99.68	2.13	1.87	32
0	1	2	0.5	99.53	0.55	0	99.53	0.55	1	226
0.2	1	2	0.5	99.34	1.03	0	99.58	1.04	1.22	70
0.5	1	2	0.5	99.50	1.24	0	99.63	1.24	2.04	91
0.8	1	2	0.5	99.44	1.23	0	99.71	1.24	2.33	119
0	2	0.5	4	99.60	0.94	0	99.60	0.94	1	226
0.2	2	0.5	4	99.59	1.89	0	99.59	1.89	1	57
0.5	2	0.5	4	99.59	3.34	0	99.59	3.34	1	19
0.8	2	0.5	4	99.68	4.78	0	99.68	4.78	1	10
0	2	1	2	99.61	0.66	0	99.61	0.66	1	226
0.2	2	1	2	99.63	1.33	0	99.63	1.33	1	57
0.5	2	1	2	99.61	2.33	0	99.63	2.33	1	19
0.8	2	1	2	99.41	3.25	0	99.68	3.26	1.07	10
0	2	2	1	99.57	0.57	0	99.57	0.57	1	226
0.2	2	2	1	99.60	1.15	0	99.61	1.15	1	57
0.5	2	2	1	99.46	1.86	0	99.62	1.88	1.30	25
0.8	2	2	1	99.44	2.10	0	99.66	2.12	1.87	32

Table 8: Adaptive three-stage Pocock-type trial: Bias and MSE of the **exact median unbiased ML estimator** given different one-sided significance levels

				$\alpha = 0.05$		$\alpha = 0.025$		$\alpha = 0.005$	
g_0	μ_E	σ^2	ϑ	Bias	MSE	Bias	MSE	Bias	MSE
0	-0.2	0.5	-0.4	-0.0049	0.0027	-0.0043	0.0026	-0.0038	0.0022
0.2	-0.2	0.5	-0.4	-0.0062	0.0064	-0.0075	0.0047	-0.0074	0.0041
0.5	-0.2	0.5	-0.4	0.0002	0.0211	-0.0079	0.0112	-0.0118	0.0076
0.8	-0.2	0.5	-0.4	-0.0009	0.0365	-0.0077	0.0234	-0.0129	0.0116
0	-0.2	1	-0.2	0.0112	0.0051	0.0060	0.0032	0.0012	0.0019
0.2	-0.2	1	-0.2	0.0188	0.0140	0.0108	0.0085	0.0027	0.0039
0.5	-0.2	1	-0.2	0.0309	0.0353	0.0182	0.0214	0.0039	0.0081
0.8	-0.2	1	-0.2	0.0441	0.0704	0.0235	0.0370	0.0036	0.0127
0	-0.2	2	-0.1	0.0305	0.0097	0.0207	0.0069	0.0132	0.0044
0.2	-0.2	2	-0.1	0.0427	0.0233	0.0291	0.0155	0.0127	0.0073
0.5	-0.2	2	-0.1	0.0565	0.0510	0.0361	0.0300	0.0171	0.0133
0.8	-0.2	2	-0.1	0.0606	0.0791	0.0411	0.0459	0.0174	0.0169
0	0	0.5	0	0.0359	0.0106	0.0334	0.0094	0.0263	0.0065
0.2	0	0.5	0	0.0632	0.0335	0.0493	0.0241	0.0310	0.0139
0.5	0	0.5	0	0.0779	0.0668	0.0585	0.0462	0.0351	0.0224
0.8	0	0.5	0	0.0906	0.1119	0.0660	0.0706	0.0374	0.0296
0	0	1	0	0.0374	0.0112	0.0346	0.0093	0.0258	0.0066
0.2	0	1	0	0.0623	0.0331	0.0513	0.0252	0.0296	0.0133
0.5	0	1	0	0.0786	0.0675	0.0600	0.0464	0.0319	0.0201
0.8	0	1	0	0.0897	0.1103	0.0672	0.0705	0.0332	0.0278
0	0	2	0	0.0358	0.0104	0.0325	0.0089	0.0263	0.0067
0.2	0	2	0	0.0646	0.0335	0.0490	0.0240	0.0302	0.0133
0.5	0	2	0	0.0780	0.0664	0.0562	0.0436	0.0356	0.0232
0.8	0	2	0	0.0972	0.1192	0.0652	0.0673	0.0335	0.0277
0	0.2	0.5	0.4	0.0002	0.0151	0.0016	0.0124	-0.0002	0.0091
0.2	0.2	0.5	0.4	0.0539	0.0410	0.0473	0.0332	0.0443	0.0255
0.5	0.2	0.5	0.4	0.1230	0.1147	0.1118	0.0992	0.0795	0.0680
0.8	0.2	0.5	0.4	0.1539	0.2068	0.1251	0.1494	0.0799	0.0936
0	0.2	1	0.2	0.0104	0.0119	0.0095	0.0096	0.0066	0.0073
0.2	0.2	1	0.2	0.0734	0.0413	0.0656	0.0343	0.0525	0.0257
0.5	0.2	1	0.2	0.1100	0.1000	0.0900	0.0765	0.0611	0.0483
0.8	0.2	1	0.2	0.1207	0.1580	0.0952	0.1064	0.0563	0.0537
0	0.2	2	0.1	0.0253	0.0104	0.0225	0.0084	0.0208	0.0066
0.2	0.2	2	0.1	0.0738	0.0405	0.0608	0.0314	0.0411	0.0198
0.5	0.2	2	0.1	0.0996	0.0872	0.0775	0.0648	0.0454	0.0309
0.8	0.2	2	0.1	0.1132	0.1406	0.0804	0.0853	0.0488	0.0427
0	0.6	0.5	1.2	-0.0011	0.0178	-0.0026	0.0144	0.0006	0.0105
0.2	0.6	0.5	1.2	-0.0060	0.0689	-0.0036	0.0565	0.0009	0.0415

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g_0	μ_E	σ^2	ϑ	$\alpha = 0.05$ Bias	MSE	$\alpha = 0.025$ Bias	MSE	$\alpha = 0.005$ Bias	MSE
0.5	0.6	0.5	1.2	0.0220	0.1644	0.0260	0.1415	0.0227	0.1007
0.8	0.6	0.5	1.2	0.1215	0.2878	0.0879	0.2097	0.1002	0.1830
0	0.6	1	0.6	-0.0031	0.0156	0.0010	0.0127	0.0007	0.0094
0.2	0.6	1	0.6	0.0224	0.0479	0.0179	0.0403	0.0149	0.0303
0.5	0.6	1	0.6	0.1177	0.1187	0.1122	0.1066	0.0924	0.0823
0.8	0.6	1	0.6	0.1662	0.2342	0.1417	0.1829	0.1001	0.1239
0	0.6	2	0.3	0.0021	0.0141	-0.0005	0.0116	0.0009	0.0086
0.2	0.6	2	0.3	0.0673	0.0405	0.0626	0.0349	0.0525	0.0257
0.5	0.6	2	0.3	0.1157	0.1086	0.1064	0.0927	0.0673	0.0570
0.8	0.6	2	0.3	0.1368	0.1833	0.1068	0.1212	0.0690	0.0759
0	1	0.5	2	-0.0009	0.0224	-0.0014	0.0185	-0.0018	0.0129
0.2	1	0.5	2	-0.0089	0.0883	-0.0105	0.0744	-0.0037	0.0532
0.5	1	0.5	2	-0.0291	0.2631	-0.0213	0.2216	-0.0134	0.1649
0.8	1	0.5	2	-0.0237	0.5121	-0.0199	0.3782	-0.0106	0.2817
0	1	1	1	-0.0013	0.0167	-0.0005	0.0137	-0.0012	0.0097
0.2	1	1	1	-0.0047	0.0654	-0.0035	0.0539	-0.0022	0.0394
0.5	1	1	1	0.0606	0.1428	0.0539	0.1185	0.0510	0.0883
0.8	1	1	1	0.1508	0.2699	0.1315	0.2093	0.1109	0.1681
0	1	2	0.5	-0.0027	0.0154	-0.0024	0.0126	-0.0006	0.0093
0.2	1	2	0.5	0.0365	0.0432	0.0324	0.0355	0.0266	0.0258
0.5	1	2	0.5	0.1245	0.1194	0.1133	0.1042	0.0916	0.0774
0.8	1	2	0.5	0.1612	0.2229	0.1320	0.1593	0.0898	0.1074
0	2	0.5	4	-0.0064	0.0451	-0.0014	0.0373	-0.0027	0.0265
0.2	2	0.5	4	-0.0139	0.1832	-0.0184	0.1461	-0.0075	0.1077
0.5	2	0.5	4	-0.0497	0.5749	-0.0378	0.4718	-0.0351	0.3340
0.8	2	0.5	4	-0.1243	1.3260	-0.0834	0.9008	-0.0635	0.7010
0	2	1	2	-0.0029	0.0220	-0.0029	0.0180	-0.0015	0.0137
0.2	2	1	2	-0.0089	0.0871	-0.0097	0.0712	-0.0050	0.0545
0.5	2	1	2	-0.0299	0.2655	-0.0251	0.2236	-0.0216	0.1626
0.8	2	1	2	-0.0194	0.5112	-0.0157	0.3630	-0.0082	0.2899
0	2	2	1	-0.0025	0.0165	-0.0011	0.0138	-0.0003	0.0100
0.2	2	2	1	-0.0023	0.0662	-0.0053	0.0542	0.0004	0.0399
0.5	2	2	1	0.0608	0.1414	0.0545	0.1163	0.0449	0.0862
0.8	2	2	1	0.1560	0.2829	0.1311	0.2095	0.1119	0.1727

Table 9: Adaptive three-stage Pocock-type trial: Bias and MSE of the **approximate median unbiased ML estimator** given different one-sided significance levels

				$\alpha = 0.05$		$\alpha = 0.025$		$\alpha = 0.005$	
g_0	μ_E	σ^2	ϑ	Bias	MSE	Bias	MSE	Bias	MSE
0	-0.2	0.5	-0.4	-0.0051	0.0028	-0.0045	0.0025	-0.0040	0.0022
0.2	-0.2	0.5	-0.4	-0.0064	0.0071	-0.0074	0.0052	-0.0078	0.0041
0.5	-0.2	0.5	-0.4	-0.0032	0.0210	-0.0097	0.0132	-0.0126	0.0079
0.8	-0.2	0.5	-0.4	0.0041	0.0481	-0.0079	0.0240	-0.0144	0.0122
0	-0.2	1	-0.2	0.0096	0.0046	0.0051	0.0031	0.0011	0.0019
0.2	-0.2	1	-0.2	0.0199	0.0144	0.0094	0.0076	0.0026	0.0039
0.5	-0.2	1	-0.2	0.0308	0.0376	0.0168	0.0228	0.0037	0.0082
0.8	-0.2	1	-0.2	0.0358	0.0607	0.0177	0.0306	0.0031	0.0131
0	-0.2	2	-0.1	0.0298	0.0097	0.0231	0.0074	0.0131	0.0044
0.2	-0.2	2	-0.1	0.0424	0.0244	0.0279	0.0152	0.0126	0.0073
0.5	-0.2	2	-0.1	0.0556	0.0503	0.0391	0.0337	0.0171	0.0135
0.8	-0.2	2	-0.1	0.0649	0.0902	0.0402	0.0468	0.0173	0.0171
0	0	0.5	0	0.0379	0.0109	0.0326	0.0088	0.0264	0.0066
0.2	0	0.5	0	0.0625	0.0331	0.0499	0.0248	0.0311	0.0140
0.5	0	0.5	0	0.0811	0.0700	0.0600	0.0470	0.0358	0.0232
0.8	0	0.5	0	0.0974	0.1199	0.0678	0.0693	0.0378	0.0303
0	0	1	0	0.0379	0.0109	0.0339	0.0092	0.0257	0.0066
0.2	0	1	0	0.0635	0.0335	0.0478	0.0235	0.0298	0.0134
0.5	0	1	0	0.0778	0.0637	0.0590	0.0448	0.0323	0.0206
0.8	0	1	0	0.0940	0.1197	0.0671	0.0714	0.0333	0.0283
0	0	2	0	0.0368	0.0109	0.0318	0.0087	0.0263	0.0067
0.2	0	2	0	0.0611	0.0322	0.0489	0.0241	0.0304	0.0135
0.5	0	2	0	0.0796	0.0677	0.0587	0.0463	0.0357	0.0233
0.8	0	2	0	0.0908	0.1123	0.0631	0.0673	0.0343	0.0289
0	0.2	0.5	0.4	-0.0013	0.0152	0.0020	0.0126	0.0000	0.0092
0.2	0.2	0.5	0.4	0.0588	0.0424	0.0496	0.0336	0.0455	0.0259
0.5	0.2	0.5	0.4	0.1326	0.1227	0.1204	0.1058	0.0821	0.0697
0.8	0.2	0.5	0.4	0.1626	0.2179	0.1257	0.1523	0.0845	0.0988
0	0.2	1	0.2	0.0109	0.0117	0.0075	0.0098	0.0067	0.0073
0.2	0.2	1	0.2	0.0725	0.0420	0.0660	0.0348	0.0533	0.0260
0.5	0.2	1	0.2	0.1148	0.1041	0.0915	0.0799	0.0627	0.0496
0.8	0.2	1	0.2	0.1380	0.1817	0.1055	0.1190	0.0579	0.0555
0	0.2	2	0.1	0.0277	0.0105	0.0238	0.0084	0.0208	0.0066
0.2	0.2	2	0.1	0.0725	0.0394	0.0630	0.0317	0.0415	0.0200
0.5	0.2	2	0.1	0.0983	0.0860	0.0780	0.0658	0.0465	0.0318
0.8	0.2	2	0.1	0.1139	0.1435	0.0795	0.0844	0.0505	0.0449
0	0.6	0.5	1.2	-0.0002	0.0174	0.0016	0.0143	0.0013	0.0105
0.2	0.6	0.5	1.2	-0.0018	0.0674	0.0014	0.0567	0.0037	0.0417

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				$\alpha = 0.05$		$\alpha = 0.025$		$\alpha = 0.005$	
g_0	μ_E	σ^2	ϑ	Bias	MSE	Bias	MSE	Bias	MSE
0.5	0.6	0.5	1.2	0.0384	0.1713	0.0309	0.1435	0.0312	0.1030
0.8	0.6	0.5	1.2	0.1561	0.3214	0.1263	0.2392	0.1180	0.1966
0	0.6	1	0.6	-0.0017	0.0157	0.0017	0.0129	0.0011	0.0094
0.2	0.6	1	0.6	0.0248	0.0493	0.0206	0.0400	0.0162	0.0305
0.5	0.6	1	0.6	0.1339	0.1333	0.1161	0.1094	0.0973	0.0855
0.8	0.6	1	0.6	0.1827	0.2634	0.1544	0.1929	0.1068	0.1310
0	0.6	2	0.3	0.0042	0.0141	0.0028	0.0116	0.0011	0.0086
0.2	0.6	2	0.3	0.0722	0.0427	0.0628	0.0349	0.0533	0.0261
0.5	0.6	2	0.3	0.1240	0.1142	0.1026	0.0906	0.0694	0.0586
0.8	0.6	2	0.3	0.1405	0.1839	0.1122	0.1292	0.0726	0.0800
0	1	0.5	2	-0.0004	0.0222	-0.0006	0.0183	-0.0007	0.0129
0.2	1	0.5	2	0.0021	0.0906	-0.0032	0.0709	0.0015	0.0534
0.5	1	0.5	2	-0.0072	0.2705	-0.0016	0.2261	0.0023	0.1675
0.8	1	0.5	2	0.0182	0.5206	0.0185	0.3933	0.0214	0.2932
0	1	1	1	-0.0013	0.0171	-0.0013	0.0138	-0.0006	0.0097
0.2	1	1	1	-0.0026	0.0654	0.0048	0.0529	0.0001	0.0396
0.5	1	1	1	0.0644	0.1402	0.0635	0.1217	0.0583	0.0913
0.8	1	1	1	0.1829	0.3097	0.1427	0.2202	0.1256	0.1811
0	1	2	0.5	0.0001	0.0155	0.0004	0.0124	-0.0003	0.0093
0.2	1	2	0.5	0.0342	0.0417	0.0337	0.0366	0.0278	0.0261
0.5	1	2	0.5	0.1336	0.1262	0.1151	0.1059	0.0955	0.0800
0.8	1	2	0.5	0.1763	0.2515	0.1408	0.1765	0.0957	0.1140
0	2	0.5	4	-0.0023	0.0449	-0.0021	0.0379	-0.0006	0.0266
0.2	2	0.5	4	-0.0029	0.1869	0.0029	0.1512	0.0034	0.1083
0.5	2	0.5	4	-0.0062	0.5830	0.0035	0.4832	-0.0011	0.3381
0.8	2	0.5	4	0.0112	1.4170	-0.0043	0.9067	0.0044	0.7198
0	2	1	2	0.0022	0.0230	-0.0005	0.0187	-0.0003	0.0137
0.2	2	1	2	-0.0041	0.0899	-0.0012	0.0725	0.0001	0.0548
0.5	2	1	2	-0.0051	0.2699	0.0054	0.2359	-0.0058	0.1642
0.8	2	1	2	0.0410	0.5310	0.0124	0.3890	0.0230	0.3013
0	2	2	1	0.0011	0.0171	-0.0004	0.0135	0.0002	0.0100
0.2	2	2	1	-0.0034	0.0649	0.0012	0.0554	0.0027	0.0401
0.5	2	2	1	0.0657	0.1397	0.0649	0.1250	0.0523	0.0893
0.8	2	2	1	0.1843	0.3260	0.1465	0.2272	0.1267	0.1859

3 Planning and Showing Superiority

We consider the one-sided significance levels $\alpha = 0.05, 0.025$, and 0.005. An adaptive five-stage O'Brien-Fleming (1979)-type design is considered for showing superiority. The critical values are constant in all stages, namely 3.915 for $\alpha = 0.05$, 4.562 for $\alpha = 0.025$, and 5.861 for $\alpha = 0.005$, see Hartung (2006).

Now $\Delta = 0$ and the value of Δ will not be changed during the course of the trial. The trial will be stopped if the lower bound of the exact (or approximate) nested confidence interval CI_k is larger than $\Delta = 0$ the first time. Note that this decision rule is the same for both intervals, the nested and the individual one.

For adaptive sample size planning, we always use a Type II error of $\beta = 0.2$. To avoid large sample sizes near the null hypothesis, we always use the maximum of 0.2 and $\hat{\vartheta} + \Delta$ in the sample size formula, see Hartung and Knapp (2009, 2010), where $\hat{\vartheta}$ denotes the (updated) median unbiased ML estimator.

Without loss of generality, we set $\mu_C = 0$. As means in the experimental group, we consider $\mu_E = 0,\ 0.2,\ 0.6, 1$, and 2 and the common variance is chosen as $\sigma^2 = 0.5,\ 1,\ 2$, so that we consider the true standardized mean differences

$$\vartheta = 0,\ 0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.5,\ 0.6,\ 1,\ 1.2,\ 2,\ 4.$$

As prior guesses of ϑ, we consider $g_0 = 0.2, 0.5$, and 0.8. In total, we simulate 45 different trials for each one-sided significance level α.

Tables 10–12 contain the results for the exact confidence intervals given one-sided significance levels of $\alpha = 0.05, 0.025$, and 0.005. Consequently, the coverage probabilities of the intervals should be at least $100(1-2\alpha)\% = 90\%, 95\%$, and 99%, respectively. Tables 13–15 contain the respective results for the approximate confidence intervals. The (mean) biases and mean-squared errors of the final exact and approximate median unbiased ML estimators are displayed in Table 16 and 17.

Again, the exact intervals always keep the nominal confidence coefficient. In case the adaptive trial passes through all five stages almost surely, the actual confidence coefficient of the nested confidence interval is close to the nominal one. Compared to the noninferiority trial, the individual confidence interval is not so conservative when the null hypothesis is true. The observed variation of the actual confidence coefficients in the superiority trial is larger than the variation in the noninferiority trial. Using a bad prior guess, that is, the starting sample size is too large, the actual confidence coefficient is nearly or exactly 100%. Like in the noninferiority trial, the difference between the average lengths of the two intervals is practically negligible.

In the adaptive five-stage O'Brien-Fleming-type trial, empty nested confidence intervals nearly never occur.

The approximate intervals also produce very satisfactory results. All the intervals keep the nominal confidence coefficient. The relationship between the nested and the individual interval is again nearly the same as for the exact intervals. The average length of the approximated intervals are comparable to those of the exact intervals. Also, the average number of performed stages and the average sample size number of the trials using the lower bound of the approximate nested confidence interval for stopping the trial are of the same magnitude as those numbers when the lower bound of the exact nested confidence interval is used for stopping the trial.

With respect to the properties of the final exact median unbiased ML estimator, the simulation study reveals the following results: Given a parameter set, the mean-squared error (MSE) of the estimator decreases with decreasing Type I error. This behavior nearly always occurs for the absolute value of the (mean) bias. Moreover, we observe a dependence of the properties of the estimator from the starting sample size; the larger the starting sample size the smaller the absolute value of the (mean) bias and the MSE. The true standard mean difference $\vartheta = 1$ seems to be the cut-off point for under- and overestimation. If the true value of ϑ is less than 1, the final exact median unbiased ML estimator on average overestimates the true parameter, while, for $\vartheta > 1$, we observe on average an underestimation.

In principle, the above statements are also valid for the final approximate median unbiased ML estimator. Generally, for $\alpha = 0.025$ and $\alpha = 0.005$, the MSE of the exact estimator is less than the MSE of the approximate estimator. But for $\alpha = 0.05$ and small starting sample size, the approximate estimator has often a lower MSE than the exact estimator.

Table 10: Adaptive five-stage O'Brien-Fleming-type trial for **showing superiority using exact confidence intervals** and one-sided significance level of $\alpha = 0.05$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.2	0	0.5	0	90.50	0.15	0.01	91.43	0.15	4.96	2001
0.5	0	0.5	0	90.38	0.19	0.08	91.20	0.19	4.96	1842
0.8	0	0.5	0	91.42	0.21	0.01	92.32	0.21	4.98	1771
0.2	0	1	0	89.80	0.15	0.03	90.88	0.15	4.96	2007
0.5	0	1	0	90.45	0.19	0.05	91.39	0.19	4.96	1845
0.8	0	1	0	91.28	0.21	0.02	92.25	0.21	4.97	1784
0.2	0	2	0	90.13	0.15	0.02	91.14	0.15	4.96	2027
0.5	0	2	0	90.58	0.19	0.05	91.57	0.19	4.97	1846
0.8	0	2	0	91.11	0.21	0.07	91.95	0.21	4.97	1782
0.2	0.2	0.5	0.4	96.90	0.73	0	97.60	0.74	3.08	123
0.5	0.2	0.5	0.4	96.31	0.76	0.01	96.97	0.77	3.76	118
0.8	0.2	0.5	0.4	96.45	0.77	0.03	97.16	0.78	3.91	132
0.2	0.2	1	0.2	94.76	0.41	0	95.60	0.41	4.08	315
0.5	0.2	1	0.2	94.10	0.44	0.08	95.10	0.44	4.44	350
0.8	0.2	1	0.2	94.19	0.45	0.12	95.17	0.46	4.56	382
0.2	0.2	2	0.1	94.01	0.25	0.01	94.92	0.26	4.70	731
0.5	0.2	2	0.1	93.21	0.29	0.10	94.20	0.29	4.82	772
0.8	0.2	2	0.1	93.70	0.31	0.07	94.52	0.31	4.87	795
0.2	0.6	0.5	1.2	99.94	1.46	0	99.94	1.46	1	68
0.5	0.6	0.5	1.2	96.64	2.00	0	97.03	2.03	2.89	20
0.8	0.6	0.5	1.2	96.72	1.89	0	97.12	1.92	3.35	23
0.2	0.6	1	0.6	97.56	1.05	0	98.01	1.06	2.27	81
0.5	0.6	1	0.6	97.08	1.08	0	97.51	1.09	3.47	63
0.8	0.6	1	0.6	97.33	1.08	0.02	97.68	1.09	3.59	70
0.2	0.6	2	0.3	95.80	0.56	0	96.63	0.58	3.51	181
0.5	0.6	2	0.3	95.36	0.59	0	96.39	0.60	4.04	187
0.8	0.6	2	0.3	94.82	0.61	0.08	95.78	0.61	4.19	210
0.2	1	0.5	2	100	1.65	0	100	1.65	1	68

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g_0	μ_E	σ^2	ϑ	Nested CI_k CC	AL	$\emptyset$	Individual I_k CC	AL	ANSt	ASN
0.5	1	0.5	2	96.36	3.40	0	96.60	3.42	1.63	13
0.8	1	0.5	2	91.11	3.07	0	91.72	3.12	2.88	10
0.2	1	1	1	99.44	1.42	0	99.55	1.42	1.06	68
0.5	1	1	1	97.30	1.67	0	97.65	1.70	3.14	27
0.8	1	1	1	97.42	1.64	0	97.75	1.66	3.38	32
0.2	1	2	0.5	97.33	0.89	0	97.80	0.90	2.71	96
0.5	1	2	0.5	96.81	0.92	0	97.50	0.94	3.57	84
0.8	1	2	0.5	96.79	0.92	0.02	97.39	0.93	3.70	94
0.2	2	0.5	4	99.99	2.33	0	99.99	2.33	1	68
0.5	2	0.5	4	99.99	5.67	0	100	5.67	1	12
0.8	2	0.5	4	96.45	6.78	0	96.78	6.82	1.77	7
0.2	2	1	2	99.99	1.65	0	99.99	1.65	1	68
0.5	2	1	2	96.11	3.40	0	96.33	3.42	1.63	13
0.8	2	1	2	91.13	3.08	0	91.84	3.13	2.87	10
0.2	2	2	1	99.58	1.41	0	99.72	1.42	1.06	68
0.5	2	2	1	97.07	1.66	0	97.45	1.69	3.15	27
0.8	2	2	1	97.80	1.62	0	98.16	1.64	3.40	32

Table 11: Adaptive five-stage O'Brien-Fleming-type trial for **showing superiority using exact confidence intervals** and one-sided significance level of $\alpha = 0.025$

g_0	μ_E	σ^2	ϑ	Nested CI_k CC	AL	$\emptyset$	Individual I_k CC	AL	ANSt	ASN
0.2	0	0.5	0	94.87	0.15	0	95.31	0.15	4.98	2553
0.5	0	0.5	0	95.13	0.18	0.01	95.59	0.18	4.98	2358
0.8	0	0.5	0	95.44	0.19	0.01	95.91	0.19	4.99	2286
0.2	0	1	0	94.92	0.15	0	95.47	0.15	4.98	2558
0.5	0	1	0	95.29	0.18	0	95.72	0.18	4.99	2375
0.8	0	1	0	95.72	0.19	0	96.06	0.19	4.99	2292
0.2	0	2	0	95.45	0.15	0.01	95.82	0.15	4.98	2548
0.5	0	2	0	95.53	0.18	0	95.86	0.18	4.98	2349
0.8	0	2	0	95.40	0.19	0	95.83	0.20	4.99	2261
0.2	0.2	0.5	0.4	98.56	0.73	0	98.84	0.74	3.05	171
0.5	0.2	0.5	0.4	97.93	0.76	0	98.26	0.76	3.90	138
0.8	0.2	0.5	0.4	98.23	0.76	0.01	98.63	0.77	4.02	149
0.2	0.2	1	0.2	97.17	0.39	0	97.72	0.40	4.17	400
0.5	0.2	1	0.2	97.30	0.42	0	97.69	0.42	4.55	415
0.8	0.2	1	0.2	97.18	0.43	0	97.61	0.44	4.63	438
0.2	0.2	2	0.1	97.42	0.25	0	97.82	0.25	4.77	898
0.5	0.2	2	0.1	96.76	0.28	0	97.20	0.28	4.88	939

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g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	Nested CI_k $\emptyset$	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.8	0.2	2	0.1	96.87	0.29	0.02	97.35	0.30	4.91	972
0.2	0.6	0.5	1.2	100	1.28	0	100	1.28	1	121
0.5	0.6	0.5	1.2	98.12	2.02	0	98.40	2.04	2.85	26
0.8	0.6	0.5	1.2	98.55	1.96	0	98.66	1.99	3.51	23
0.2	0.6	1	0.6	99.09	1.04	0	99.27	1.05	1.86	128
0.5	0.6	1	0.6	98.76	1.09	0	98.92	1.10	3.62	70
0.8	0.6	1	0.6	98.54	1.09	0	98.71	1.10	3.74	78
0.2	0.6	2	0.3	97.75	0.56	0	98.24	0.57	3.56	235
0.5	0.6	2	0.3	97.80	0.58	0	98.20	0.59	4.15	222
0.8	0.6	2	0.3	97.70	0.59	0	98.14	0.60	4.28	236
0.2	1	0.5	2	100	1.44	0	100	1.44	1	121
0.5	1	0.5	2	98.90	3.40	0	98.96	3.40	1.25	21
0.8	1	0.5	2	95.96	3.23	0	96.42	3.27	2.69	13
0.2	1	1	1	99.98	1.25	0	99.98	1.25	1	121
0.5	1	1	1	98.51	1.70	0	98.66	1.72	3.21	32
0.8	1	1	1	98.50	1.67	0	98.62	1.69	3.61	32
0.2	1	2	0.5	98.61	0.89	0	98.84	0.90	2.50	142
0.5	1	2	0.5	98.27	0.92	0	98.54	0.93	3.74	96
0.8	1	2	0.5	98.19	0.93	0	98.53	0.94	3.86	104
0.2	2	0.5	4	100	2.02	0	100	2.02	1	121
0.5	2	0.5	4	100	5.06	0	100	5.06	1	20
0.8	2	0.5	4	99.20	7.39	0	99.20	7.39	1.16	9
0.2	2	1	2	100	1.44	0	100	1.44	1	121
0.5	2	1	2	98.89	3.40	0	98.98	3.40	1.25	21
0.8	2	1	2	95.61	3.20	0	96.01	3.24	2.70	13
0.2	2	2	1	99.97	1.25	0	99.97	1.25	1	121
0.5	2	2	1	98.23	1.69	0	98.45	1.72	3.22	32
0.8	2	2	1	98.68	1.66	0	98.77	1.68	3.61	32

Table 12: Adaptive five-stage O'Brien-Fleming-type trial for **showing superiority using exact confidence intervals** and one-sided significance level of $\alpha = 0.005$

g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	Nested CI_k $\emptyset$	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.2	0	0.5	0	99.01	0.15	0	99.10	0.15	5	3609
0.5	0	0.5	0	99.04	0.18	0	99.10	0.18	5	3401
0.8	0	0.5	0	99.18	0.19	0	99.20	0.19	5	3314
0.2	0	1	0	98.95	0.15	0	99.00	0.15	5	3617
0.5	0	1	0	98.81	0.18	0	98.88	0.18	5	3409

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				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.8	0	1	0	99.10	0.19	0	99.15	0.19	5	3302
0.2	0	2	0	98.88	0.15	0	98.94	0.15	5	3605
0.5	0	2	0	99.10	0.17	0	99.16	0.18	5	3400
0.8	0	2	0	98.99	0.19	0	99.08	0.19	5	3271
0.2	0.2	0.5	0.4	99.62	0.74	0	99.71	0.75	3.77	208
0.5	0.2	0.5	0.4	99.69	0.76	0	99.70	0.77	4.24	189
0.8	0.2	0.5	0.4	99.52	0.77	0	99.60	0.77	4.31	210
0.2	0.2	1	0.2	99.51	0.39	0	99.56	0.39	4.53	554
0.5	0.2	1	0.2	99.33	0.41	0	99.39	0.41	4.74	602
0.8	0.2	1	0.2	99.50	0.43	0	99.58	0.43	4.79	628
0.2	0.2	2	0.1	99.34	0.25	0	99.39	0.25	4.93	1308
0.5	0.2	2	0.1	99.39	0.27	0	99.44	0.27	4.97	1377
0.8	0.2	2	0.1	99.37	0.28	0	99.44	0.28	4.98	1429
0.2	0.6	0.5	1.2	100	1.64	0	100	1.64	1	121
0.5	0.6	0.5	1.2	99.49	2.01	0	99.52	2.04	3.77	31
0.8	0.6	0.5	1.2	99.71	2.01	0	99.72	2.03	4.06	30
0.2	0.6	1	0.6	99.76	1.09	0	99.79	1.10	3.04	141
0.5	0.6	1	0.6	99.60	1.10	0	99.65	1.11	4.06	94
0.8	0.6	1	0.6	99.68	1.11	0	99.77	1.12	4.07	105
0.2	0.6	2	0.3	99.47	0.56	0	99.56	0.57	4.09	311
0.5	0.6	2	0.3	99.46	0.59	0	99.51	0.59	4.43	314
0.8	0.6	2	0.3	99.44	0.60	0	99.49	0.60	4.50	334
0.2	1	0.5	2	100	1.85	0	100	1.85	1	121
0.5	1	0.5	2	99.04	3.43	0	99.13	3.46	2.30	23
0.8	1	0.5	2	98.86	3.15	0	98.92	3.19	3.63	15
0.2	1	1	1	99.92	1.59	0	99.92	1.59	1.08	121
0.5	1	1	1	99.77	1.72	0	99.80	1.74	3.94	39
0.8	1	1	1	99.78	1.71	0	99.82	1.73	4.04	43
0.2	1	2	0.5	99.70	0.91	0	99.73	0.92	3.48	164
0.5	1	2	0.5	99.67	0.94	0	99.69	0.95	4.12	128
0.8	1	2	0.5	99.65	0.95	0	99.68	0.95	4.16	143
0.2	2	0.5	4	100	2.59	0	100	2.59	1	121
0.5	2	0.5	4	100	6.48	0	100	6.48	1	20
0.8	2	0.5	4	98.40	6.83	0	98.42	6.86	2.04	11
0.2	2	1	2	100	1.85	0	100	1.85	1	121
0.5	2	1	2	99.21	3.44	0	99.33	3.46	2.30	23
0.8	2	1	2	98.63	3.15	0	98.69	3.19	3.63	15
0.2	2	2	1	99.89	1.58	0	99.91	1.59	1.08	121
0.5	2	2	1	99.70	1.71	0	99.74	1.73	3.93	40
0.8	2	2	1	99.70	1.71	0	99.72	1.72	4.03	44

Table 13: Adaptive five-stage O'Brien-Fleming-type trial for **showing superiority using approximate confidence intervals** and one-sided significance level of $\alpha = 0.05$

				Nested CI_k			Individual I_k			
g_0	μ_E	σ^2	ϑ	CC	AL	$\emptyset$	CC	AL	ANSt	ASN
0.2	0	0.5	0	90.15	0.17	0.02	91.19	0.17	4.96	1248
0.5	0	0.5	0	90.58	0.21	0	91.53	0.21	4.96	1116
0.8	0	0.5	0	91.64	0.24	0	92.41	0.24	4.98	1056
0.2	0	1	0	90.15	0.17	0.01	91.10	0.17	4.96	1249
0.5	0	1	0	90.77	0.21	0	91.77	0.21	4.96	1117
0.8	0	1	0	91.40	0.24	0	92.37	0.24	4.97	1050
0.2	0	2	0	89.78	0.17	0	90.73	0.17	4.95	1245
0.5	0	2	0	90.64	0.21	0	91.63	0.21	4.97	1114
0.8	0	2	0	91.41	0.23	0	92.18	0.24	4.98	1052
0.2	0.2	0.5	0.4	96.45	0.74	0	97.26	0.75	3.08	123
0.5	0.2	0.5	0.4	96.60	0.77	0	97.38	0.78	3.78	119
0.8	0.2	0.5	0.4	96.13	0.78	0.01	96.87	0.79	3.96	131
0.2	0.2	1	0.2	94.71	0.40	0.01	95.58	0.41	4.09	316
0.5	0.2	1	0.2	94.79	0.44	0.01	95.72	0.45	4.45	338
0.8	0.2	1	0.2	94.57	0.45	0.02	95.39	0.45	4.58	371
0.2	0.2	2	0.1	93.55	0.26	0	94.63	0.26	4.70	688
0.5	0.2	2	0.1	93.66	0.30	0	94.52	0.30	4.82	687
0.8	0.2	2	0.1	93.65	0.32	0	94.35	0.32	4.87	691
0.2	0.6	0.5	1.2	99.92	1.46	0	99.93	1.46	1	68
0.5	0.6	0.5	1.2	97.13	2.05	0.01	97.44	2.08	3.04	20
0.8	0.6	0.5	1.2	97.42	1.91	0	97.76	1.93	3.58	23
0.2	0.6	1	0.6	97.40	1.05	0	97.99	1.07	2.28	81
0.5	0.6	1	0.6	97.39	1.09	0	97.88	1.10	3.49	62
0.8	0.6	1	0.6	97.55	1.07	0	98.04	1.08	3.64	71
0.2	0.6	2	0.3	95.87	0.57	0	96.76	0.58	3.51	181
0.5	0.6	2	0.3	95.70	0.60	0	96.72	0.61	4.05	186
0.8	0.6	2	0.3	95.79	0.61	0	96.60	0.62	4.21	204
0.2	1	0.5	2	99.99	1.65	0	99.99	1.65	1	68
0.5	1	0.5	2	97.50	3.48	0	97.87	3.50	1.73	14
0.8	1	0.5	2	94.28	3.06	0	95.04	3.09	3.35	11
0.2	1	1	1	99.56	1.42	0	99.65	1.42	1.06	68
0.5	1	1	1	97.49	1.71	0	97.73	1.73	3.26	26
0.8	1	1	1	97.79	1.63	0	98.13	1.65	3.56	31
0.2	1	2	0.5	97.54	0.90	0	97.99	0.92	2.69	95
0.5	1	2	0.5	96.94	0.93	0	97.55	0.94	3.61	84
0.8	1	2	0.5	96.97	0.93	0	97.51	0.94	3.77	92
0.2	2	0.5	4	99.97	2.35	0	99.97	2.35	1	68

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g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	Nested CI_k ∅	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.5	2	0.5	4	100	5.86	0	100	5.86	1	12
0.8	2	0.5	4	94.88	6.46	0	95.01	6.50	2.25	8
0.2	2	1	2	100	1.65	0	100	1.65	1	68
0.5	2	1	2	97.38	3.49	0	97.69	3.50	1.74	14
0.8	2	1	2	94.30	3.05	0	95.06	3.08	3.36	11
0.2	2	2	1	99.58	1.42	0	99.70	1.42	1.06	68
0.5	2	2	1	97.26	1.69	0	97.65	1.71	3.27	27
0.8	2	2	1	97.48	1.62	0.01	97.83	1.64	3.57	32

Table 14: Adaptive five-stage O'Brien-Fleming-type trial for **showing superiority using approximate confidence intervals** and one-sided significance level of $\alpha = 0.025$

g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	Nested CI_k ∅	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.2	0	0.5	0	94.84	0.17	0	95.32	0.17	4.98	1411
0.5	0	0.5	0	95.44	0.21	0	95.92	0.21	4.99	1258
0.8	0	0.5	0	95.76	0.24	0	96.14	0.24	4.99	1194
0.2	0	1	0	95.45	0.17	0	95.83	0.17	4.99	1409
0.5	0	1	0	95.45	0.21	0	95.83	0.21	4.99	1259
0.8	0	1	0	95.83	0.24	0	96.16	0.24	4.99	1194
0.2	0	2	0	95.30	0.17	0	95.74	0.18	4.98	1406
0.5	0	2	0	95.30	0.21	0	95.78	0.22	4.99	1253
0.8	0	2	0	95.83	0.24	0	96.18	0.24	4.99	1197
0.2	0.2	0.5	0.4	98.46	0.74	0	98.83	0.75	3.34	150
0.5	0.2	0.5	0.4	98.25	0.77	0	98.55	0.78	3.97	140
0.8	0.2	0.5	0.4	98.23	0.78	0	98.58	0.79	4.11	153
0.2	0.2	1	0.2	97.63	0.39	0	98.04	0.40	4.29	389
0.5	0.2	1	0.2	97.27	0.42	0	97.69	0.43	4.59	422
0.8	0.2	1	0.2	97.43	0.44	0	97.91	0.44	4.68	444
0.2	0.2	2	0.1	97.00	0.25	0	97.36	0.26	4.81	829
0.5	0.2	2	0.1	96.93	0.29	0	97.40	0.29	4.90	837
0.8	0.2	2	0.1	96.63	0.31	0	97.05	0.31	4.93	831
0.2	0.6	0.5	1.2	99.97	1.53	0	99.97	1.53	1	84
0.5	0.6	0.5	1.2	98.43	2.02	0	98.59	2.05	3.47	24
0.8	0.6	0.5	1.2	98.73	1.95	0	98.89	1.96	3.85	26
0.2	0.6	1	0.6	98.78	1.08	0	98.92	1.09	2.53	99
0.5	0.6	1	0.6	98.71	1.09	0	98.92	1.11	3.72	72
0.8	0.6	1	0.6	98.64	1.09	0	98.89	1.10	3.78	83
0.2	0.6	2	0.3	97.91	0.57	0	98.38	0.58	3.74	220

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g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	Nested CI_k $\emptyset$	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.5	0.6	2	0.3	97.87	0.60	0.01	98.34	0.60	4.21	226
0.8	0.6	2	0.3	97.57	0.61	0	98.05	0.61	4.35	244
0.2	1	0.5	2	100	1.73	0	100	1.73	1	84
0.5	1	0.5	2	97.77	3.51	0	97.93	3.53	2.07	16
0.8	1	0.5	2	96.65	3.08	0	96.94	3.11	3.71	12
0.2	1	1	1	99.77	1.49	0	99.80	1.49	1.07	84
0.5	1	1	1	98.82	1.71	0	98.96	1.73	3.60	31
0.8	1	1	1	98.86	1.66	0	99.02	1.67	3.81	36
0.2	1	2	0.5	98.49	0.91	0	98.69	0.92	3.00	116
0.5	1	2	0.5	98.39	0.94	0	98.61	0.95	3.82	98
0.8	1	2	0.5	98.38	0.93	0	98.64	0.94	3.95	108
0.2	2	0.5	4	100	2.46	0	100	2.46	1	84
0.5	2	0.5	4	99.98	6.27	0	99.98	6.27	1	14
0.8	2	0.5	4	97.68	6.45	0	97.71	6.48	2.57	9
0.2	2	1	2	100	1.73	0	100	1.73	1	84
0.5	2	1	2	98.03	3.50	0	98.21	3.52	2.08	16
0.8	2	1	2	96.59	3.06	0	96.95	3.09	3.72	13
0.2	2	2	1	99.69	1.48	0	99.77	1.48	1.07	84
0.5	2	2	1	98.87	1.71	0	98.97	1.73	3.63	30
0.8	2	2	1	99.05	1.67	0	99.11	1.68	3.81	35

Table 15: Adaptive five-stage O'Brien-Fleming-type trial for **showing superiority using approximate confidence intervals** and one-sided significance level of $\alpha = 0.005$

g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	Nested CI_k $\emptyset$	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.2	0	0.5	0	99.12	0.20	0	99.23	0.20	5	1641
0.5	0	0.5	0	99.02	0.23	0	99.05	0.23	5	1460
0.8	0	0.5	0	99.18	0.25	0	99.26	0.25	5	1389
0.2	0	1	0	98.99	0.20	0	99.06	0.20	5	1639
0.5	0	1	0	98.90	0.23	0	98.97	0.23	5	1457
0.8	0	1	0	99.20	0.25	0	99.23	0.25	5	1386
0.2	0	2	0	99.14	0.20	0	99.19	0.20	5	1640
0.5	0	2	0	98.81	0.23	0	98.90	0.23	5	1464
0.8	0	2	0	99.22	0.25	0	99.28	0.25	5	1392
0.2	0.2	0.5	0.4	99.62	0.75	0	99.66	0.76	3.76	208
0.5	0.2	0.5	0.4	99.58	0.77	0	99.60	0.78	4.24	191
0.8	0.2	0.5	0.4	99.70	0.78	0	99.72	0.78	4.32	204
0.2	0.2	1	0.2	99.51	0.39	0	99.58	0.40	4.53	551

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g_0	μ_E	σ^2	ϑ	Nested CI_k CC	Nested CI_k AL	$\emptyset$	Individual I_k CC	Individual I_k AL	ANSt	ASN
0.5	0.2	1	0.2	99.47	0.41	0	99.53	0.42	4.75	589
0.8	0.2	1	0.2	99.38	0.43	0	99.46	0.43	4.80	615
0.2	0.2	2	0.1	99.35	0.25	0	99.40	0.25	4.92	1146
0.5	0.2	2	0.1	99.37	0.28	0	99.42	0.28	4.97	1138
0.8	0.2	2	0.1	99.47	0.30	0	99.52	0.30	4.98	1103
0.2	0.6	0.5	1.2	100	1.64	0	100	1.64	1	121
0.5	0.6	0.5	1.2	99.71	2.03	0	99.73	2.05	3.99	32
0.8	0.6	0.5	1.2	99.72	2.01	0	99.79	2.03	4.26	30
0.2	0.6	1	0.6	99.74	1.09	0	99.76	1.10	3.07	141
0.5	0.6	1	0.6	99.69	1.12	0	99.71	1.13	4.05	95
0.8	0.6	1	0.6	99.74	1.12	0	99.76	1.13	4.09	104
0.2	0.6	2	0.3	99.60	0.57	0	99.67	0.57	4.07	309
0.5	0.6	2	0.3	99.52	0.59	0	99.56	0.59	4.42	313
0.8	0.6	2	0.3	99.60	0.60	0	99.65	0.60	4.50	329
0.2	1	0.5	2	100	1.85	0	100	1.85	1	121
0.5	1	0.5	2	99.40	3.47	0	99.45	3.48	2.60	23
0.8	1	0.5	2	99.24	3.11	0	99.28	3.13	4.26	17
0.2	1	1	1	99.92	1.59	0	99.93	1.59	1.07	121
0.5	1	1	1	99.82	1.74	0	99.83	1.76	4.06	39
0.8	1	1	1	99.73	1.73	0	99.73	1.74	4.14	43
0.2	1	2	0.5	99.64	0.92	0	99.68	0.93	3.46	163
0.5	1	2	0.5	99.67	0.95	0	99.68	0.96	4.13	128
0.8	1	2	0.5	99.69	0.95	0	99.75	0.96	4.20	141
0.2	2	0.5	4	100	2.63	0	100	2.63	1	121
0.5	2	0.5	4	100	6.63	0	100	6.63	1	20
0.8	2	0.5	4	98.95	6.40	0	98.99	6.43	2.92	13
0.2	2	1	2	100	1.85	0	100	1.85	1	121
0.5	2	1	2	99.39	3.46	0	99.44	3.48	2.61	23
0.8	2	1	2	99.25	3.10	0	99.28	3.12	4.26	17
0.2	2	2	1	99.93	1.59	0	99.94	1.59	1.08	121
0.5	2	2	1	99.74	1.74	0	99.76	1.76	4.07	39
0.8	2	2	1	99.81	1.73	0	99.82	1.74	4.13	43

Table 16: Adaptive five-stage O'Brien-Fleming-type trial: Bias and MSE of the **exact median unbiased ML estimator** given different one-sided significance levels

g_0	μ_E	σ^2	ϑ	$\alpha = 0.05$ Bias	$\alpha = 0.05$ MSE	$\alpha = 0.025$ Bias	$\alpha = 0.025$ MSE	$\alpha = 0.005$ Bias	$\alpha = 0.005$ MSE
0.2	0	0.5	0	0.0154	0.0048	0.0097	0.0025	0.0057	0.0013

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g_0	μ_E	σ^2	ϑ	$\alpha = 0.05$ Bias	$\alpha = 0.05$ MSE	$\alpha = 0.025$ Bias	$\alpha = 0.025$ MSE	$\alpha = 0.005$ Bias	$\alpha = 0.005$ MSE
0.5	0	0.5	0	0.0254	0.0137	0.0164	0.0068	0.0087	0.0027
0.8	0	0.5	0	0.0279	0.0215	0.0183	0.0093	0.0105	0.0042
0.2	0	1	0	0.0149	0.0050	0.0089	0.0024	0.0052	0.0012
0.5	0	1	0	0.0258	0.0158	0.0153	0.0065	0.0087	0.0031
0.8	0	1	0	0.0272	0.0202	0.0190	0.0099	0.0110	0.0048
0.2	0	2	0	0.0145	0.0048	0.0092	0.0023	0.0057	0.0012
0.5	0	2	0	0.0243	0.0140	0.0157	0.0067	0.0088	0.0028
0.8	0	2	0	0.0295	0.0242	0.0205	0.0107	0.0110	0.0042
0.2	0.2	0.5	0.4	0.0434	0.0276	0.0313	0.0176	0.0273	0.0165
0.5	0.2	0.5	0.4	0.0619	0.0579	0.0477	0.0395	0.0348	0.0262
0.8	0.2	0.5	0.4	0.0662	0.0735	0.0506	0.0486	0.0357	0.0318
0.2	0.2	1	0.2	0.0434	0.0195	0.0288	0.0114	0.0204	0.0076
0.5	0.2	1	0.2	0.0552	0.0387	0.0394	0.0217	0.0271	0.0135
0.8	0.2	1	0.2	0.0591	0.0521	0.0454	0.0298	0.0314	0.0168
0.2	0.2	2	0.1	0.0292	0.0115	0.0206	0.0068	0.0124	0.0037
0.5	0.2	2	0.1	0.0408	0.0247	0.0296	0.0148	0.0181	0.0071
0.8	0.2	2	0.1	0.0456	0.0350	0.0340	0.0192	0.0203	0.0095
0.2	0.6	0.5	1.2	-0.0003	0.0349	-0.0035	0.0199	-0.0016	0.0194
0.5	0.6	0.5	1.2	-0.0229	0.1655	-0.0422	0.1190	-0.0633	0.0988
0.8	0.6	0.5	1.2	-0.0469	0.2102	-0.0482	0.1502	-0.0591	0.1056
0.2	0.6	1	0.6	0.0271	0.0285	0.0159	0.0169	0.0155	0.0192
0.5	0.6	1	0.6	0.0528	0.0790	0.0416	0.0547	0.0302	0.0404
0.8	0.6	1	0.6	0.0577	0.0997	0.0443	0.0668	0.0289	0.0457
0.2	0.6	2	0.3	0.0452	0.0242	0.0327	0.0153	0.0243	0.0123
0.5	0.6	2	0.3	0.0580	0.0463	0.0437	0.0304	0.0322	0.0197
0.8	0.6	2	0.3	0.0627	0.0653	0.0481	0.0379	0.0347	0.0232
0.2	1	0.5	2	-0.0008	0.0438	-0.0022	0.0248	-0.0037	0.0255
0.5	1	0.5	2	-0.0501	0.3099	-0.0234	0.1682	-0.1229	0.2499
0.8	1	0.5	2	-0.2270	0.6173	-0.1812	0.4330	-0.2659	0.3934
0.2	1	1	1	0.0028	0.0325	-0.0012	0.0185	-0.0002	0.0192
0.5	1	1	1	0.0025	0.1283	-0.0085	0.0916	-0.0236	0.0685
0.8	1	1	1	0.0062	0.1766	-0.0129	0.1119	-0.0152	0.0757
0.2	1	2	0.5	0.0375	0.0284	0.0240	0.0178	0.0214	0.0185
0.5	1	2	0.5	0.0602	0.0731	0.0464	0.0483	0.0357	0.0345
0.8	1	2	0.5	0.0609	0.0873	0.0478	0.0588	0.0379	0.0418
0.2	2	0.5	4	-0.0127	0.0894	-0.0032	0.0509	-0.0017	0.0506
0.5	2	0.5	4	-0.0548	0.5545	-0.0365	0.3219	-0.0365	0.3211
0.8	2	0.5	4	-0.3496	2.2219	-0.0836	0.8473	-0.4277	1.3402
0.2	2	1	2	-0.0023	0.0457	-0.0022	0.0245	-0.0042	0.0252
0.5	2	1	2	-0.0468	0.3082	-0.0181	0.1717	-0.1237	0.2494

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g_0	μ_E	σ^2	ϑ	$\alpha = 0.05$ Bias	$\alpha = 0.05$ MSE	$\alpha = 0.025$ Bias	$\alpha = 0.025$ MSE	$\alpha = 0.005$ Bias	$\alpha = 0.005$ MSE
0.8	2	1	2	-0.2282	0.6272	-0.1919	0.4418	-0.2672	0.4011
0.2	2	2	1	-0.0018	0.0322	-0.0008	0.0189	-0.0048	0.0191
0.5	2	2	1	-0.0053	0.1190	-0.0104	0.0898	-0.0280	0.0688
0.8	2	2	1	-0.0051	0.1503	-0.0163	0.1052	-0.0205	0.0750

Table 17: Adaptive five-stage O'Brien-Fleming trial: Bias and MSE of the **approximate median unbiased ML estimator** given different one-sided significance levels

g_0	μ_E	σ^2	ϑ	$\alpha = 0.05$ Bias	$\alpha = 0.05$ MSE	$\alpha = 0.025$ Bias	$\alpha = 0.025$ MSE	$\alpha = 0.005$ Bias	$\alpha = 0.005$ MSE
0.2	0	0.5	0	0.0114	0.0050	0.0060	0.0033	0.0017	0.0017
0.5	0	0.5	0	0.0203	0.0152	0.0123	0.0092	0.0046	0.0037
0.8	0	0.5	0	0.0235	0.0202	0.0154	0.0132	0.0050	0.0059
0.2	0	1	0	0.0116	0.0052	0.0062	0.0031	0.0022	0.0019
0.5	0	1	0	0.0205	0.0151	0.0108	0.0082	0.0041	0.0039
0.8	0	1	0	0.0236	0.0210	0.0130	0.0122	0.0048	0.0054
0.2	0	2	0	0.0119	0.0055	0.0072	0.0034	0.0021	0.0017
0.5	0	2	0	0.0199	0.0145	0.0126	0.0096	0.0029	0.0040
0.8	0	2	0	0.0227	0.0196	0.0142	0.0140	0.0047	0.0062
0.2	0.2	0.5	0.4	0.0472	0.0282	0.0394	0.0231	0.0302	0.0167
0.5	0.2	0.5	0.4	0.0641	0.0582	0.0553	0.0465	0.0380	0.0278
0.8	0.2	0.5	0.4	0.0659	0.0684	0.0546	0.0488	0.0404	0.0317
0.2	0.2	1	0.2	0.0422	0.0191	0.0305	0.0132	0.0215	0.0082
0.5	0.2	1	0.2	0.0579	0.0382	0.0413	0.0249	0.0267	0.0132
0.8	0.2	1	0.2	0.0535	0.0415	0.0434	0.0280	0.0297	0.0160
0.2	0.2	2	0.1	0.0284	0.0112	0.0221	0.0082	0.0116	0.0040
0.5	0.2	2	0.1	0.0423	0.0262	0.0286	0.0157	0.0133	0.0068
0.8	0.2	2	0.1	0.0437	0.0339	0.0306	0.0208	0.0171	0.0094
0.2	0.6	0.5	1.2	-0.0013	0.0353	0.0038	0.0284	-0.0006	0.0194
0.5	0.6	0.5	1.2	-0.0228	0.1578	-0.0508	0.1197	-0.0710	0.0826
0.8	0.6	0.5	1.2	-0.0565	0.1491	-0.0599	0.1240	-0.0608	0.0815
0.2	0.6	1	0.6	0.0284	0.0274	0.0245	0.0233	0.0145	0.0182
0.5	0.6	1	0.6	0.0516	0.0711	0.0425	0.0559	0.0347	0.0412
0.8	0.6	1	0.6	0.0477	0.0761	0.0389	0.0611	0.0362	0.0457
0.2	0.6	2	0.3	0.0470	0.0249	0.0375	0.0190	0.0271	0.0130
0.5	0.6	2	0.3	0.0610	0.0462	0.0507	0.0357	0.0330	0.0200
0.8	0.6	2	0.3	0.0644	0.0572	0.0541	0.0408	0.0361	0.0224
0.2	1	0.5	2	0.0019	0.0449	-0.0001	0.0364	0.0008	0.0251
0.5	1	0.5	2	-0.0326	0.3077	-0.0608	0.2903	-0.1248	0.2288

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				$\alpha = 0.05$		$\alpha = 0.025$		$\alpha = 0.005$	
g_0	μ_E	σ^2	ϑ	Bias	MSE	Bias	MSE	Bias	MSE
0.8	1	0.5	2	-0.2620	0.4864	-0.2752	0.4333	-0.2788	0.3294
0.2	1	1	1	-0.0009	0.0332	0.0023	0.0271	0.0008	0.0181
0.5	1	1	1	0.0011	0.1120	-0.0142	0.0865	-0.0210	0.0570
0.8	1	1	1	-0.0102	0.1126	-0.0176	0.0896	-0.0142	0.0659
0.2	1	2	0.5	0.0390	0.0281	0.0324	0.0240	0.0250	0.0184
0.5	1	2	0.5	0.0583	0.0644	0.0538	0.0548	0.0404	0.0352
0.8	1	2	0.5	0.0592	0.0725	0.0467	0.0517	0.0370	0.0377
0.2	2	0.5	4	0.0005	0.0911	0.0015	0.0743	0.0035	0.0499
0.5	2	0.5	4	-0.0037	0.5595	-0.0029	0.4870	-0.0038	0.3211
0.8	2	0.5	4	-0.4184	1.4920	-0.4412	1.4089	-0.4747	1.1819
0.2	2	1	2	-0.0008	0.0449	0.0018	0.0367	-0.0017	0.0247
0.5	2	1	2	-0.0263	0.3136	-0.0678	0.2863	-0.1280	0.2352
0.8	2	1	2	-0.2644	0.5113	-0.2830	0.4321	-0.2840	0.3318
0.2	2	2	1	0.0017	0.0331	-0.0002	0.0268	0.0011	0.0188
0.5	2	2	1	-0.0076	0.1109	-0.0130	0.0865	-0.0198	0.0613
0.8	2	2	1	-0.0138	0.1168	-0.0152	0.0871	-0.0162	0.0633

4 Final Remarks

In an extensive simulation study, we have investigated the practical properties of final repeated confidence intervals and point estimates for the standardized mean difference in adaptive group sequential trials as proposed by Hartung and Knapp (2009, 2010). They suggest exact and approximate confidence intervals and point estimates. The computation of the exact confidence interval and point estimate involves the solution of nonlinear equations containing the cumulative distribution function of the noncentral t-distribution, whereas the approximate confidence interval and point estimate are explicitly given. The simulation study reveals that the approximate solutions are very close to the exact solutions. From a practical point of view, the approximate solutions can be recommended because of their accuracy and simplicity.

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