Design and analysis of three-arm trials with negative binomially distributed endpoints
- Supplementary Material -

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Contents

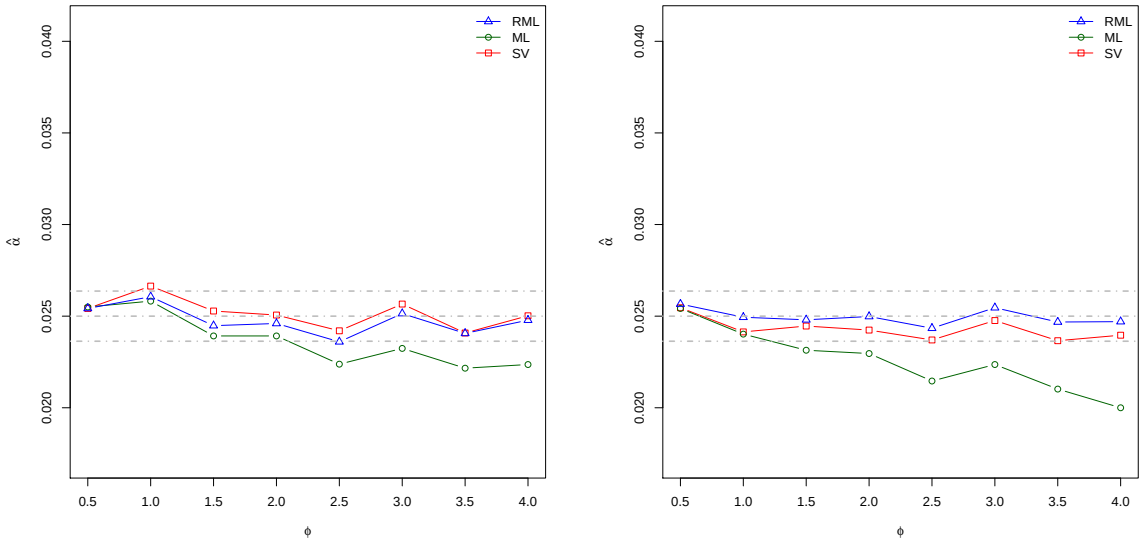
1 Level of significance

This section provides the remaining graphics from the simulation study not shown in the publication. The complete setup of the simulation study is shown in Table 1. The results are based on 50 000 simulations.

Table 1: Scenarios considered in the Monte-Carlo simulation study for the significance level.

Parameter	**Values**
Significance Level α	0.025
Clinical relevance margin Δ	0.6, 0.7, 0.8, 0.9, 1.05, 1.1, 1.15, 1.2
Rates (λ_R, λ_P)	(3.4, 11.6), (5.1, 17.4), (7.65, 26.1)
Total Sample size n	150, 200, 250, ..., 400, 450
Sample size allocation $n_E : n_R : n_P$	1:1:1, 2:1:1, 2:2:1, 3:2:1
Shape parameter ϕ	0.5, 1, ..., 3.5, 4

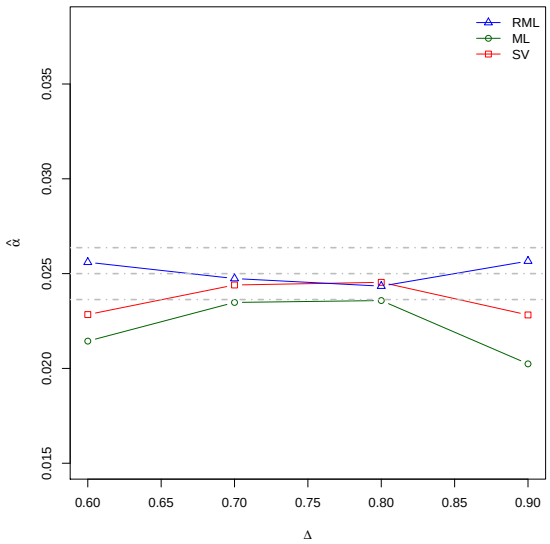
1.1 Simulation results for $(\lambda_R, \lambda_P) = (5.1, 17.4)$



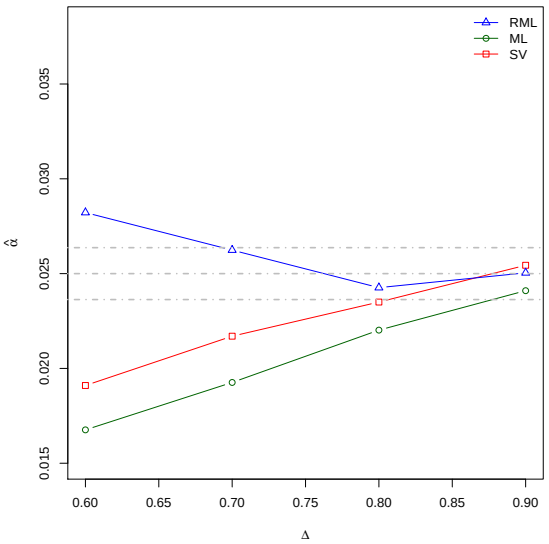
Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$

Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

Figure 1: Simulated level of significance $\hat{\alpha}$ versus the shape parameter ϕ for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The total sample size n and the margin Δ are fixed to $n = 400$ and $\Delta = 0.8$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



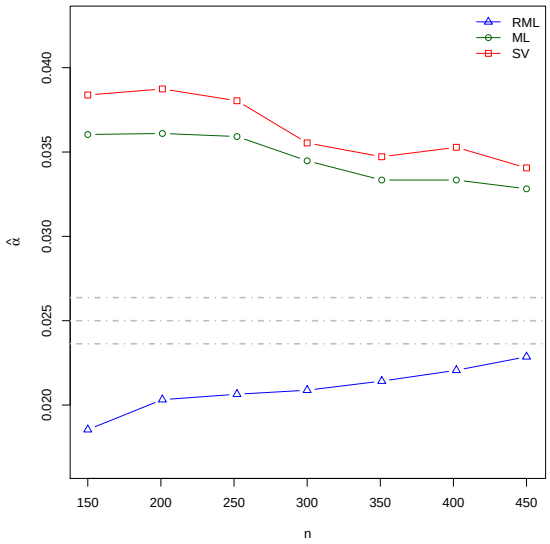
Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$



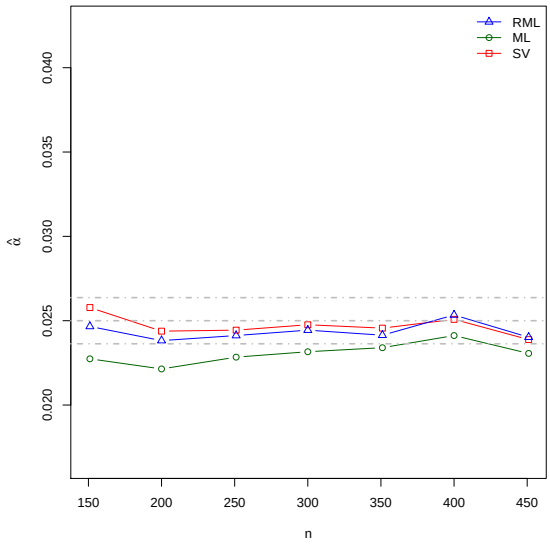
Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

Figure 2: Simulated level of significance $\hat{\alpha}$ versus the margin Δ for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The total sample size n and the shape parameter ϕ are fixed to $n = 400$ and $\phi = 2$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.

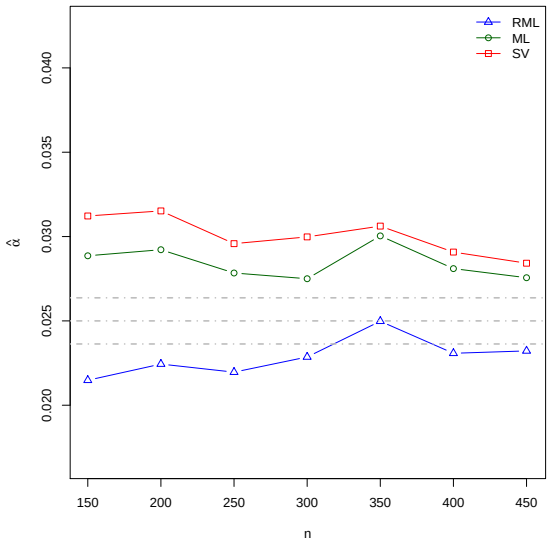
1.2 Simulation results for $(\lambda_R, \lambda_P) = (3.4, 11.6)$



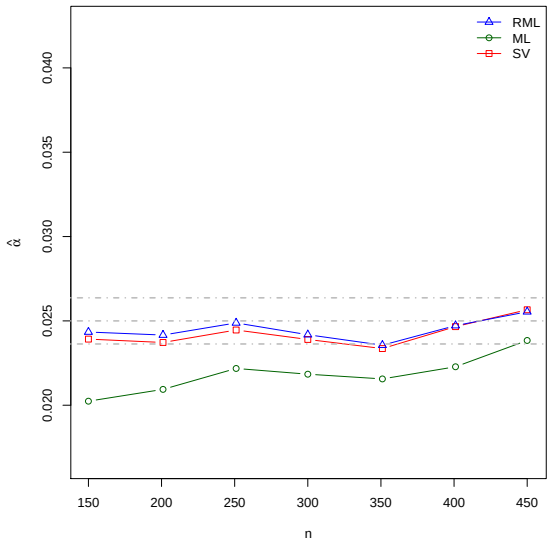
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$

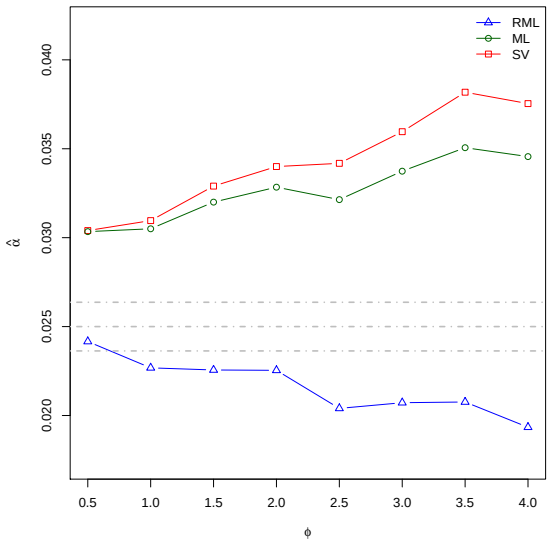


Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$

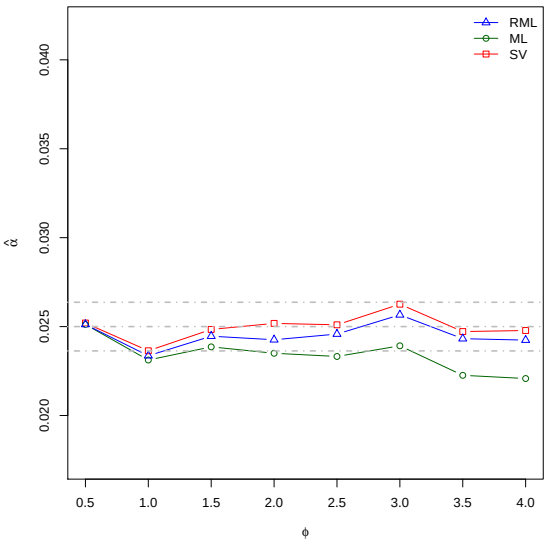


Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

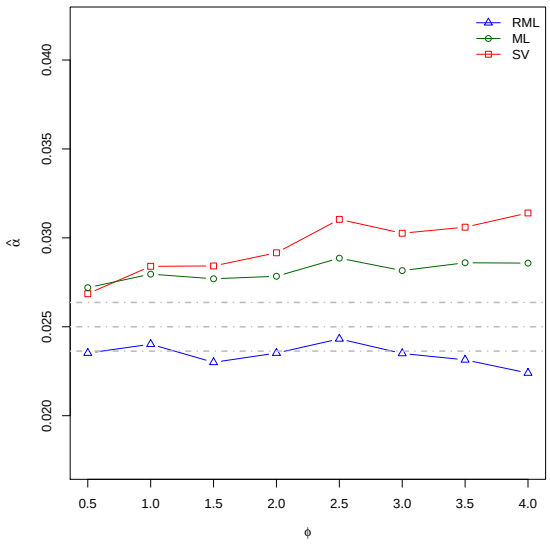
Figure 3: Simulated level of significance $\hat{\alpha}$ versus the total sample size n for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The shape parameter ϕ and the margin Δ are fixed to $\phi = 2$ and $\Delta = 0.8$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



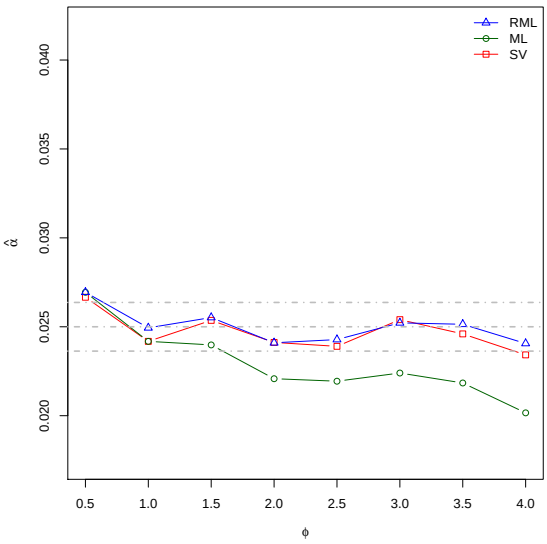
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$

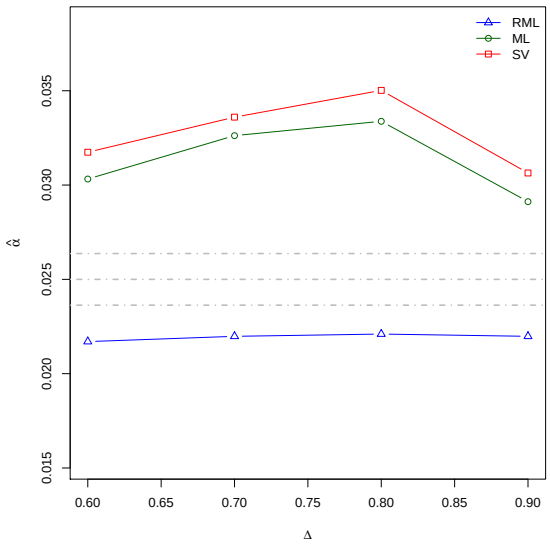


Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$

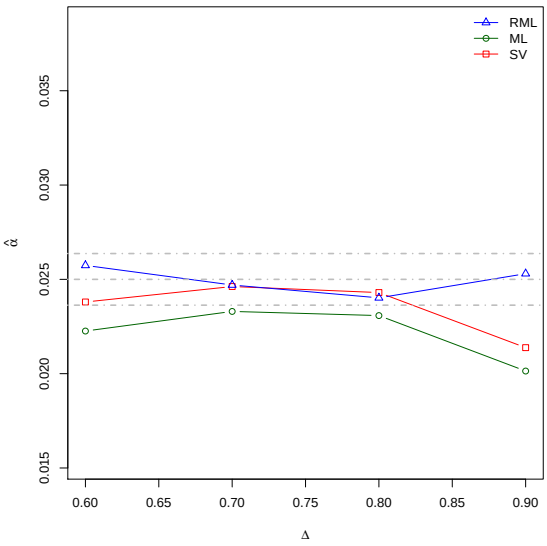


Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

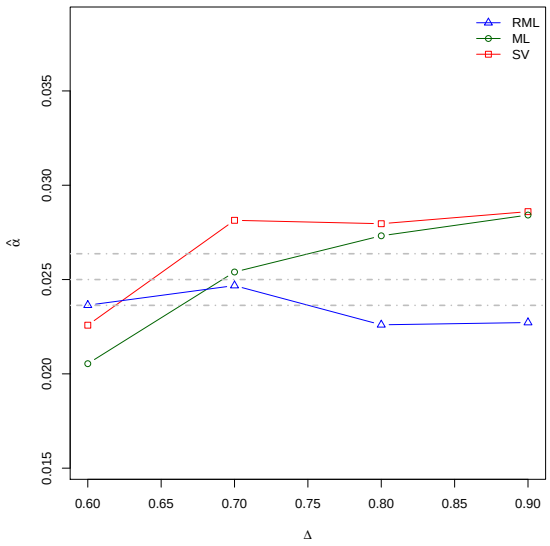
Figure 4: Simulated level of significance $\hat{\alpha}$ versus the shape parameter ϕ for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The total sample size n and the margin Δ are fixed to $n = 400$ and $\Delta = 0.8$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



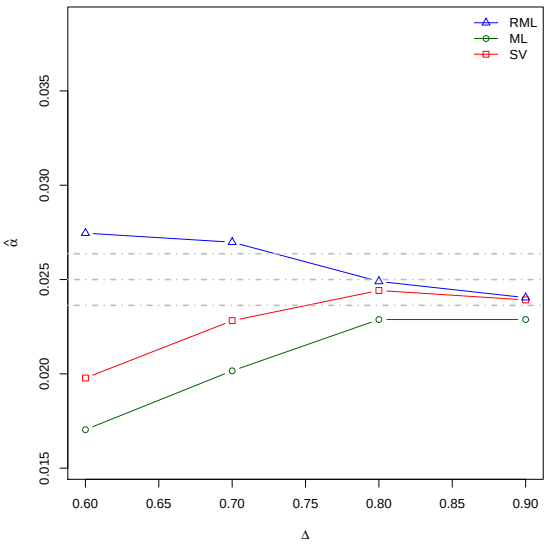
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$

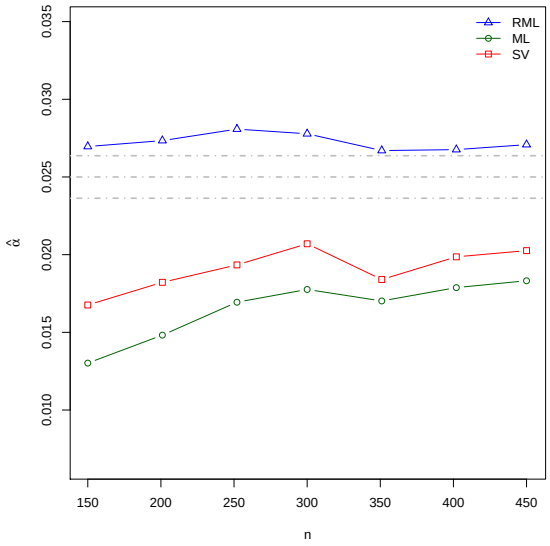


Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$

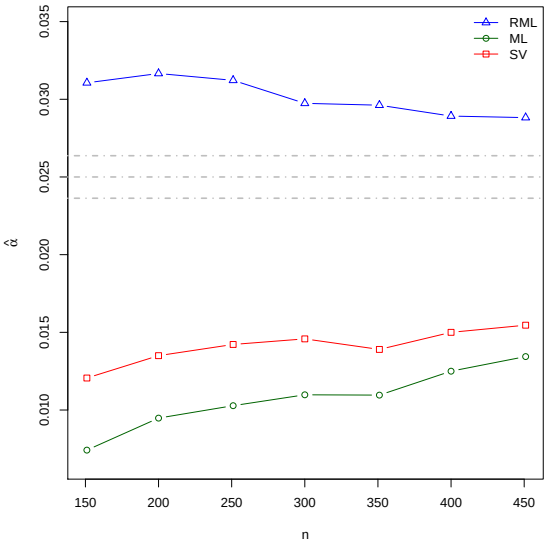


Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

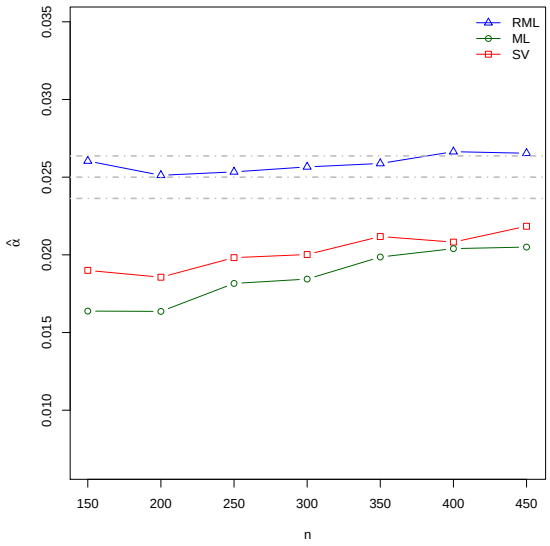
Figure 5: Simulated level of significance $\hat{\alpha}$ versus the non-inferiority parameter Δ for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The total sample size n and the shape parameter ϕ are fixed to $n = 400$ and $\phi = 2$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



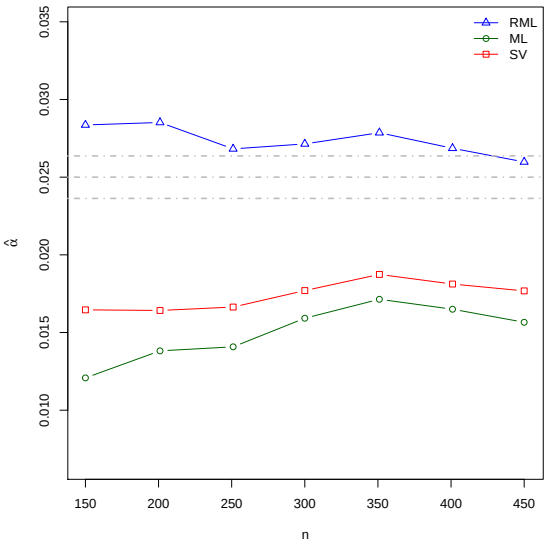
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$



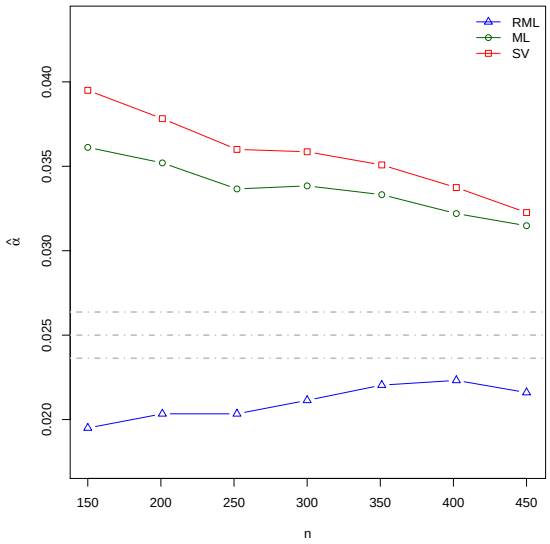
Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$



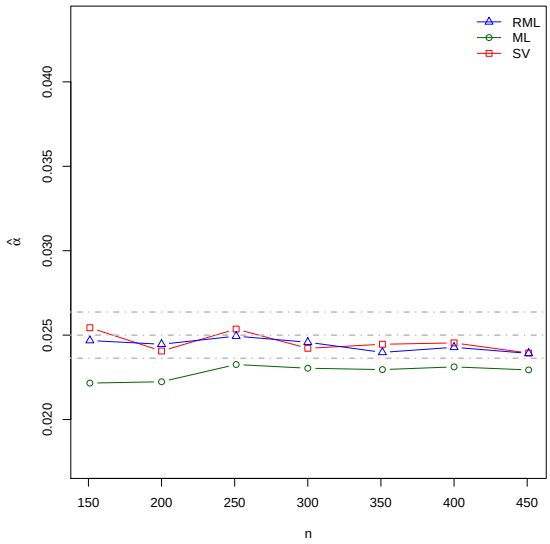
Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

Figure 6: Simulated level of significance $\hat{\alpha}$ versus the total sample size n for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The shape parameter ϕ and the margin Δ are fixed to $\phi = 2$ and $\Delta = 1.1$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.

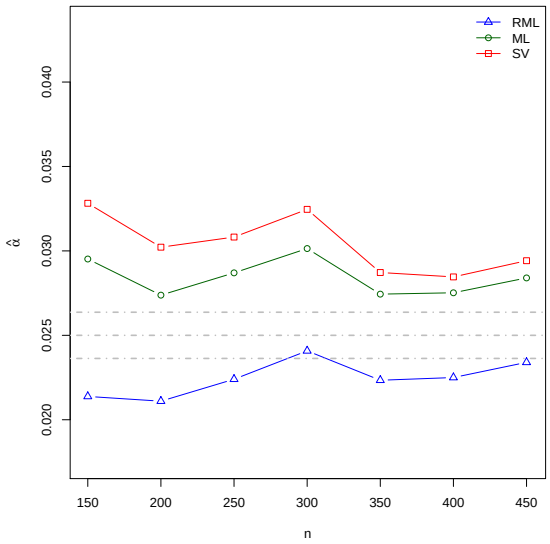
1.3 Simulation results for $(\lambda_R, \lambda_P) = (7.65, 26.1)$



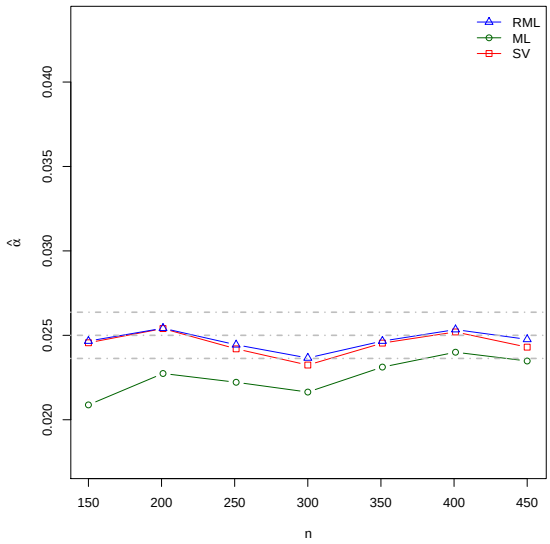
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$

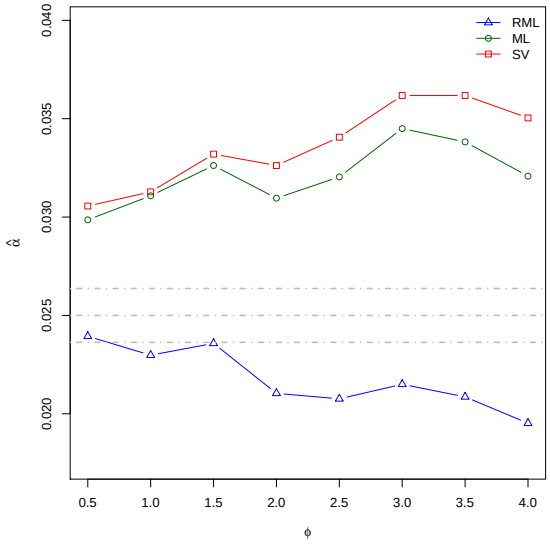


Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$

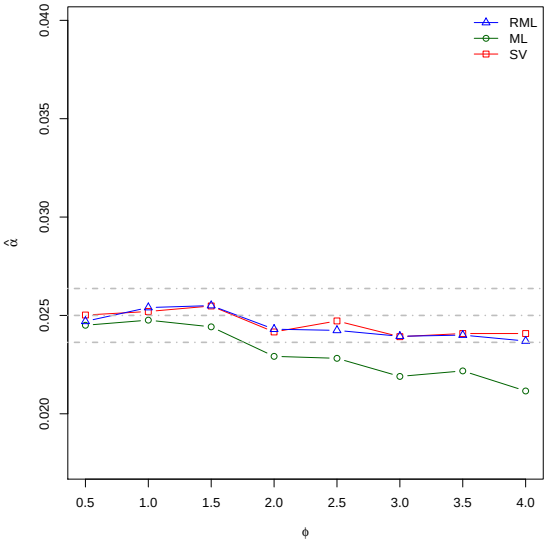


Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

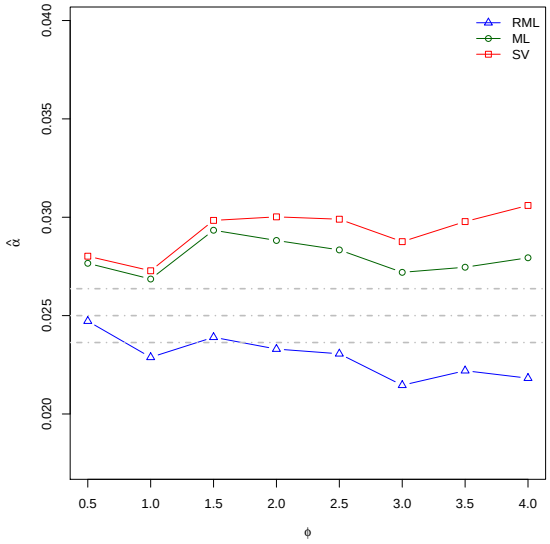
Figure 7: Simulated level of significance $\hat{\alpha}$ versus the total sample size n for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The shape parameter ϕ and the margin Δ are fixed to $\phi = 2$ and $\Delta = 0.8$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



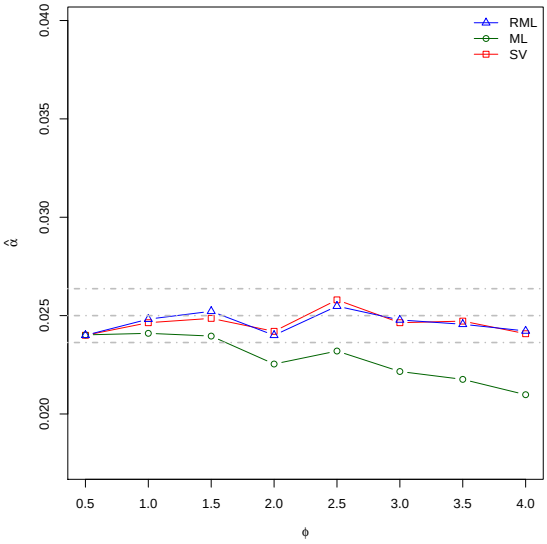
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$

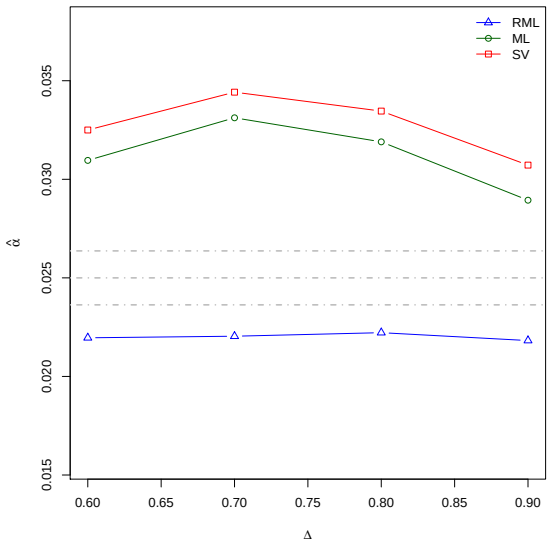


Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$

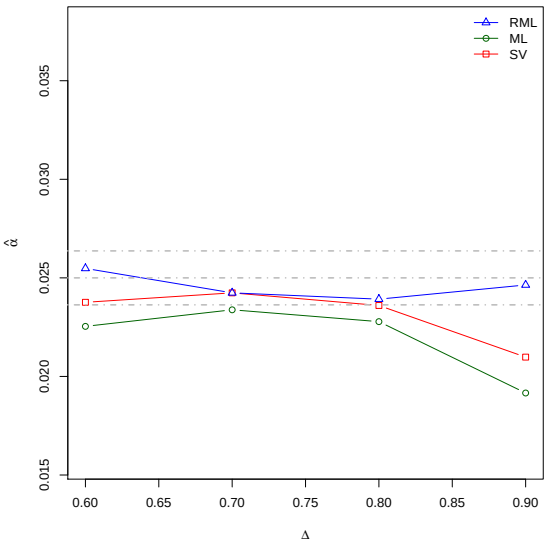


Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

Figure 8: Simulated level of significance $\hat{\alpha}$ versus the shape parameter ϕ for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The total sample size n and the margin Δ are fixed to $n = 400$ and $\Delta = 0.8$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



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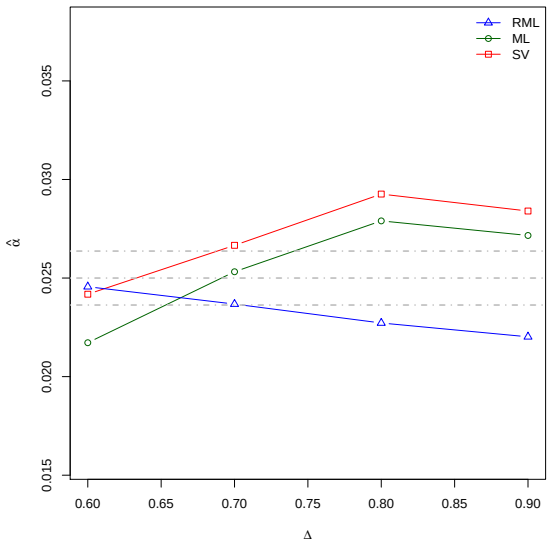
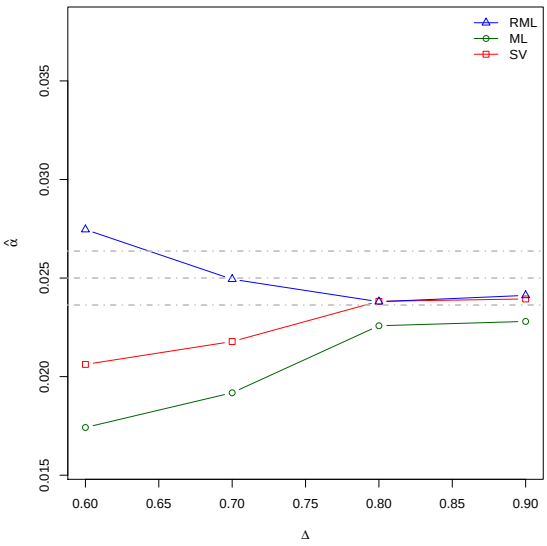
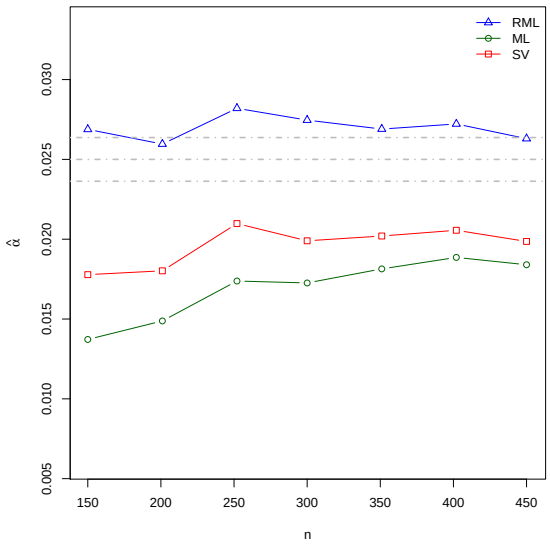


Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$

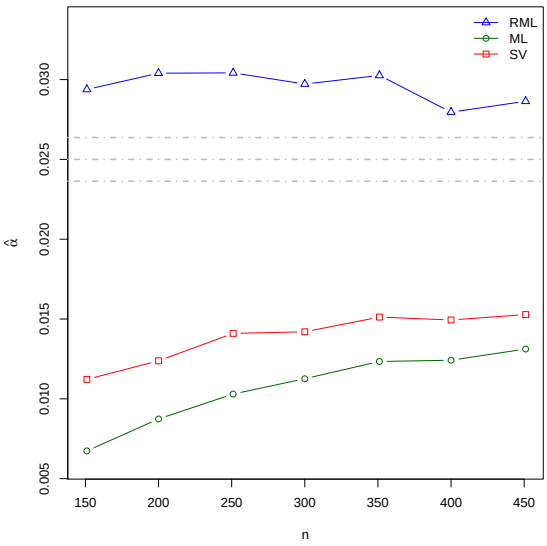


Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

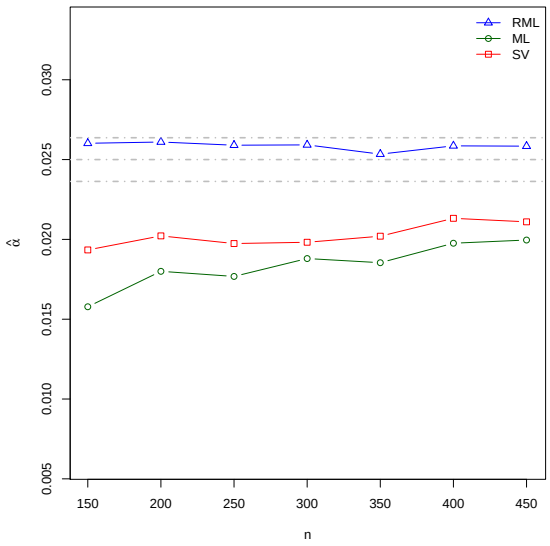
Figure 9: Simulated level of significance $\hat{\alpha}$ versus the non-inferiority parameter Δ for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The total sample size n and the shape parameter ϕ are fixed to $n = 400$ and $\phi = 2$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.



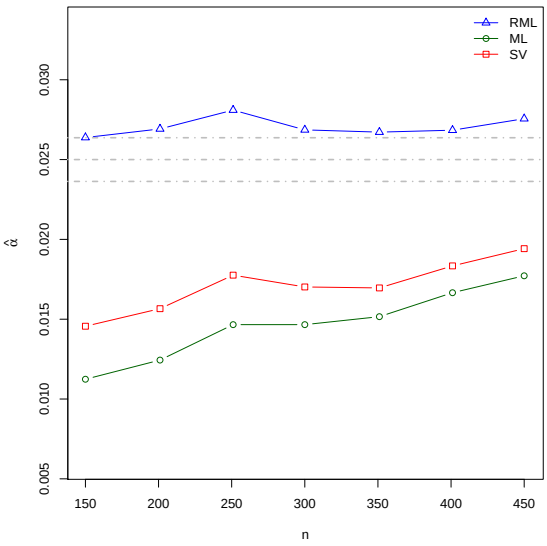
Sample Size Allocation $n_E : n_R : n_P = 1 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 1 : 1$



Sample Size Allocation $n_E : n_R : n_P = 2 : 2 : 1$



Sample Size Allocation $n_E : n_R : n_P = 3 : 2 : 1$

Figure 10: Simulated level of significance $\hat{\alpha}$ versus the total sample size n for the Wald-type test with the restricted maximum-likelihood variance estimator (RML), the unrestricted maximum-likelihood variance estimator (ML), and the sample variance estimator (SV). The shape parameter ϕ and the margin Δ are fixed to $\phi = 2$ and $\Delta = 1.1$, respectively. The dashed horizontal lines indicate $\alpha = 0.025$ and the area in which the simulated level is expected.

2 Power and Sample Size Allocation

2.1 Simulation results for $(\lambda_R, \lambda_P) = (5.1, 17.4)$

Table 2: Simulated power of the Wald-type test with a restricted maximum-likelihood variance estimator for the alternative $\lambda_E = \lambda_R = 5.1$, $\lambda_P = 17.4$, and $\alpha = 0.025$.

Sample Size Allocation	**Δ**	**n**	**ϕ**	**Power RML**	**Power ML**	Ratio
3:2:1	0.7	148	1	0.8340	0.8107	1.0287
	0.8	255		0.8181	0.8130	1.0063
	0.9	812		0.8054	0.8043	1.0014
	0.7	274	2	0.8242	0.7914	1.0414
	0.8	471		0.8124	0.8040	1.0104
	0.9	1497		0.8047	0.8027	1.0024
	0.7	400	3	0.8274	0.7930	1.0434
	0.8	687		0.8116	0.8020	1.0119
	0.9	2182		0.8002	0.7985	1.0021
2:1:1	0.7	136	1	0.8279	0.8248	1.0038
	0.8	249		0.8151	0.8135	1.0020
	0.9	880		0.8071	0.7979	1.0115
	0.7	252	2	0.8225	0.8144	1.0100
	0.8	460		0.8111	0.8075	1.0044
	0.9	1620		0.8048	0.7944	1.0131
	0.7	368	3	0.8247	0.8145	1.0125
	0.8	672		0.8114	0.8065	1.0061
	0.9	2359		0.8025	0.7934	1.0115

2.2 Simulation results for $(\lambda_R, \lambda_P) = (3.4, 11.6)$

Figure 11 shows the results of a simulation study for the optimal sample size allocation of the Wald-type test with a restricted maximum-likelihood variance estimator for non-inferiority for the following parameters: rates $\lambda_E = \lambda_R = 3.4$, and $\lambda_P = 11.6$, shape parameter $\phi = 2$, and non-inferiority margin $\Delta = 0.8$. The sample size is determined to be $n = 487$ which corresponds to a trial with a power of around 81.32% for the chosen

Table 3: Simulated power of the Wald-type test with a restricted maximum-likelihood variance estimator for the alternative $\lambda_E = \lambda_R = 3.4$, $\lambda_P = 11.6$, and $\alpha = 0.025$.

Sample Size Allocation	**Δ**	**n**	ϕ	**Power RML**	**Power ML**	Ratio
3:2:1	0.7	156	1	0.8302	0.8079	1.0276
	0.8	271		0.8176	0.8138	1.0047
	0.9	873		0.8040	0.8031	1.0012
	0.7	283	2	0.8265	0.7949	1.0397
	0.8	487		0.8132	0.8061	1.0088
	0.9	1558		0.8070	0.8053	1.0021
	0.7	408	3	0.8236	0.7904	1.0420
	0.8	704		0.8122	0.8035	1.0109
	0.9	2244		0.8060	0.8042	1.0023
2:1:1	0.7	144	1	0.8279	0.8258	1.0025
	0.8	268		0.8177	0.8165	1.0014
	0.9	951		0.8078	0.7981	1.0121
	0.7	260	2	0.8257	0.8188	1.0084
	0.8	480		0.8118	0.8087	1.0039
	0.9	1688		0.7995	0.7896	1.0125
	0.7	376	3	0.8237	0.8144	1.0114
	0.8	689		0.8089	0.8046	1.0053
	0.9	2428		0.8045	0.7944	1.0127

rates, shape parameter, margin, and a sample size allocation of 3:2:1 as shown in Table 3. During the Monte-Carlo simulation, the Wald-type test is performed with the level of significance $\alpha = 0.025$. The optimal sample size allocation for the Wald-type test with the unrestricted maximum-likelihood estimator is $w_{opt}n = (0.4080, 0.3264, 0.2655)n \approx (199, 159, 129)$. The numerical maximization of the power formula (3) of the Wald-type test with the restricted maximum-likelihood estimator gives the sample size allocation $w_{opt}^{RML}n = (0.5359, 0.2567, 0.2074)n \approx (261, 125, 101)$. During the simulation study, the power for every possible sample size $(n - n_R - n_P, n_R, n_P)$ with $n_R = 55, 65, \ldots, 195$ and $n_P = 31, 41, \ldots, 171$ is simulated using 50 000 Monte-Carlo simulations per sample size vector. The optimal sample size allocation obtained through the Monte-Carlo simulations is $w_{opt}^{MC}n = (261, 135, 91)$ with a power of 82.28%. Figure 11 shows a contour plot of the simulated power in dependence of the sample size allocation in the reference treatment and the placebo group.

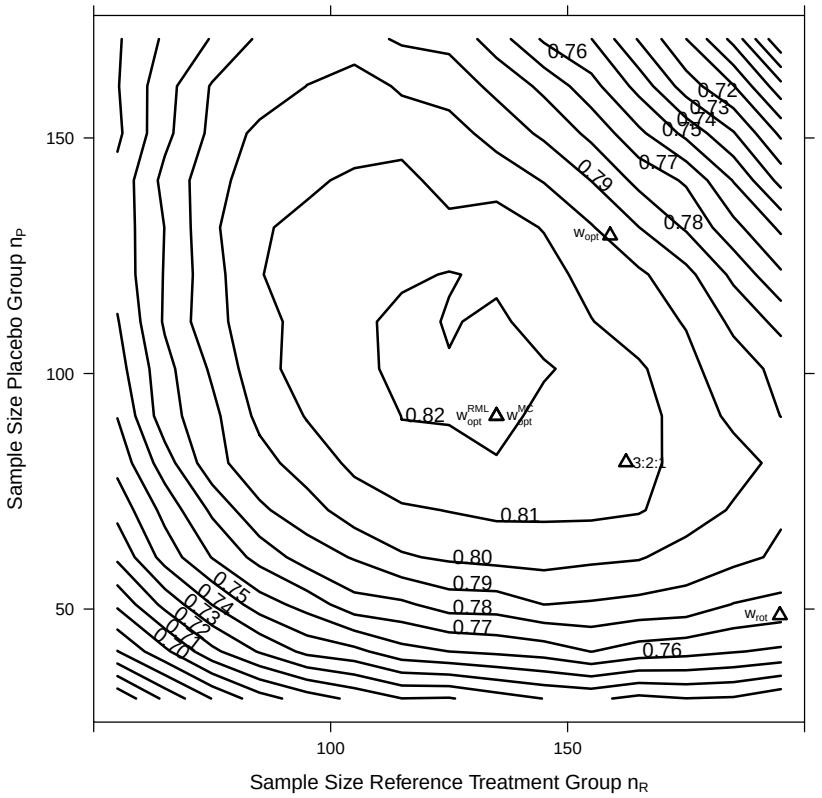


Figure 11: Simulated power the Wald-type tests with a restricted maximum-likelihood variance estimator for the sample size $n = 487$. The sample size of the placebo group is shown on the y-axis while the sample size of the reference treatment group is shown on the x-axis. Different sample size allocations are marked as triangles.

2.3 Simulation results for $(\lambda_R, \lambda_P) = (7.65, 26.1)$

Table 4: Simulated power of the Wald-type test with a restricted maximum-likelihood variance estimator for the alternative $\lambda_E = \lambda_R = 7.65$, $\lambda_P = 26.1$, and $\alpha = 0.025$.

Sample Size Allocation	**Δ**	**n**	**ϕ**	**Power RML**	**Power ML**	Ratio
3:2:1	0.7	142	1	0.8316	0.8057	1.0322
	0.8	243		0.8183	0.8118	1.0080
	0.9	771		0.8034	0.8024	1.0013
	0.7	268	2	0.8283	0.7948	1.0421
	0.8	459		0.8114	0.8027	1.0108
	0.9	1456		0.8061	0.8044	1.0021
	0.7	394	3	0.8266	0.7917	1.0440
	0.8	676		0.8137	0.8037	1.0124
	0.9	2141		0.8043	0.8023	1.0025
2:1:1	0.7	132	1	0.8307	0.8265	1.0052
	0.8	240		0.8180	0.8165	1.0019
	0.9	836		0.8051	0.7960	1.0114
	0.7	248	2	0.8278	0.8188	1.0110
	0.8	449		0.8128	0.8089	1.0048
	0.9	1572		0.8026	0.7923	1.0131
	0.7	361	3	0.8240	0.8129	1.0136
	0.8	660		0.8111	0.8068	1.0052
	0.9	2312		0.8068	0.7968	1.0126

Figure 12 shows the results of a simulation study for the optimal sample size allocation of the Wald-type test with a restricted maximum-likelihood variance estimator for non-inferiority for the following parameters: rates $\lambda_E = \lambda_R = 7.65$, and $\lambda_P = 26.1$, shape parameter $\phi = 2$, and non-inferiority margin $\Delta = 0.8$. The sample size is determined to be $n = 459$ which corresponds to a trial with a power of around 81.32% for the chosen rates, shape parameter, margin, and a sample size allocation of 3:2:1 as shown in Table 4. During the Monte-Carlo simulation, the Wald-type test is performed with the level of significance $\alpha = 0.025$. The optimal sample size allocation for the Wald-type test with the unrestricted maximum-likelihood estimator is $w_{opt}n = (0.4053, 0.3242, 0.2705)n \approx$

(186, 149, 124). The numerical maximization of the power formula (3) of the Wald-type test with the restricted maximum-likelihood estimator gives the sample size allocation $w_{opt}^{RML} n = (0.5359, 0.2527, 0.2113)n \approx (246, 116, 97)$. During the simulation study, the power for every possible sample size $(n - n_R - n_P, n_R, n_P)$ with $n_R = 46, 56, \ldots, 186$ and $n_P = 27, 37, \ldots, 167$ is simulated using 50 000 Monte-Carlo simulations per sample size vector. The optimal sample size allocation obtained through the Monte-Carlo simulations is $w_{opt}^{MC} n = (246, 126, 87)$ with a power of 82.32%. Figure 12 shows a contour plot of the simulated power in dependence of the sample size allocation in the reference treatment and the placebo group.

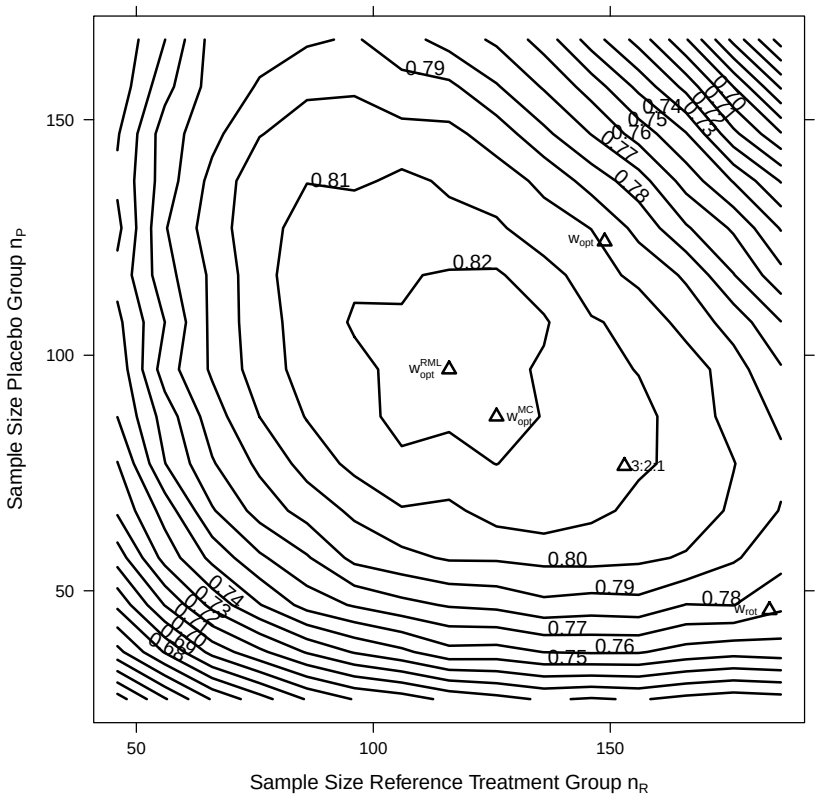


Figure 12: Simulated power the Wald-type tests with a restricted maximum-likelihood variance estimator for the sample size $n = 459$. The sample size of the placebo group is shown on the y-axis while the sample size of the reference treatment group is shown on the x-axis. Different sample size allocations are marked as triangles.