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Web Appendix

Impact of correlation structure on sample size requirements of statistical methods for multiple binary outcomes: A simulation study

Table S1. Summary of simulation methods

A) Scenarios with null treatment effects	
Sample size	200 per arm
Number of components K	2, 3, 4, 5, 6, 7, 8, 9, 10
Treatment effects $\pi_{k,e} - \pi_{k,c}$ for $k = 1, \dots, K$	0% (common)
Marginal proportions in the control arm $\pi_{k,c}$ for $k = 1, \dots, K$	20% (common), 60% (common)
Correlation $\rho_e = \rho_c$	0, 0.45, 0.9
B) Scenarios with two or more components	
Sample size	200 per arm
Number of components K	2, 3, 4, 5, 6, 7, 8, 9, 10
Treatment effects $\pi_{k,e} - \pi_{k,c}$ for $k = 1, \dots, K$	5% (common), 10% (common), 15% (common)
Marginal proportions in the control arm $\pi_{k,c}$ for $k = 1, \dots, K$	20% (common), 60% (common)
Correlation $\rho_e = \rho_c$	0, 0.45, 0.9
C) Scenarios with two components	
Sample size	200 per arm
Number of components K	2
Treatment effects $(\pi_{1,e} - \pi_{1,c}, \pi_{2,e} - \pi_{2,c})$	(10%, 10%), (10%, 0%), (0%, 0%), (15%, -5%), (-5%, 15%)
Marginal proportions in the control arm $(\pi_{1,c}, \pi_{2,c})$	(20%, 40%), (60%, 40%)
Correlation ρ_e and ρ_c	$\rho_e \in \{-0.9, -0.45, 0, 0.45, 0.9\}$ and $\rho_c \in \{-0.9, -0.45, 0, 0.45, 0.9\}$

Outcome generation: To create correlated outcomes, K -dimensional Gaussian variables $Y_{1,a}^*, \dots, Y_{K,a}^*$ with a mean vector $(\Phi^{-1}(\pi_{1,a}), \dots, \Phi^{-1}(\pi_{K,a}))$, variances 1, and pairwise correlations ρ_a were generated for the 200 experimental and 200 control subjects ($a = e, c$), where $\Phi(\cdot)$ is the cumulative distribution function of the standard Gaussian distribution. The binary outcomes $Y_{1,a}, \dots, Y_{K,a}$ were derived by discretizing $Y_{1,a}^*, \dots, Y_{K,a}^*$ such that $Y_{k,a} = 1$ if $Y_{k,a}^* > 0$ and $Y_{k,a} = 0$ otherwise. This Gaussian copula-based method achieves the marginal proportions $\Pr[Y_{k,a} = 1] = \pi_{k,a}$ regardless of the correlation ρ_a . The degree of outcome overlapping is higher with stronger positive correlations.

Table S2. Type I error rate in the simulation

Correlation	Number of components	Co-primary	Multiple primary	Composite[all]	Composite[$\geq K/2$]	Net benefit
A) Marginal proportions in the control arm: 20%						
0	2	0.05%	2.53%	2.41%	2.52%	2.44%
	3	0.00%	2.43%	1.51%	2.47%	2.50%
	4	0.00%	2.53%	0.03%	2.52%	2.55%
	5	0.00%	2.40%	0.00%	2.49%	2.43%
	6	0.00%	2.39%	0.00%	2.52%	2.42%
	7	0.00%	2.55%	0.00%	2.49%	2.62%
	8	0.00%	2.40%	0.00%	2.48%	2.41%
	9	0.00%	2.47%	0.00%	2.23%	2.52%
	10	0.00%	2.44%	0.00%	2.48%	2.57%
0.45	2	0.21%	2.46%	2.52%	2.52%	2.52%
	3	0.03%	2.41%	2.49%	2.52%	2.46%
	4	0.01%	2.41%	2.37%	2.53%	2.53%
	5	0.00%	2.26%	2.26%	2.54%	2.53%
	6	0.00%	2.26%	2.27%	2.51%	2.51%
	7	0.00%	2.37%	2.14%	2.53%	2.48%
	8	0.00%	2.25%	1.70%	2.48%	2.45%
	9	0.00%	2.28%	1.34%	2.51%	2.49%
	10	0.00%	2.20%	0.90%	2.49%	2.45%
0.9	2	0.82%	2.24%	2.64%	2.64%	2.59%
	3	0.43%	2.00%	2.51%	2.63%	2.58%
	4	0.25%	1.86%	2.53%	2.52%	2.48%
	5	0.20%	1.75%	2.52%	2.53%	2.49%
	6	0.17%	1.58%	2.52%	2.51%	2.45%
	7	0.12%	1.67%	2.51%	2.57%	2.48%
	8	0.07%	1.53%	2.56%	2.49%	2.43%
	9	0.08%	1.49%	2.51%	2.44%	2.43%
	10	0.08%	1.49%	2.56%	2.62%	2.55%
B) Marginal proportions in the control arm: 60%						
0	2	0.07%	2.50%	2.59%	2.60%	2.51%
	3	0.00%	2.49%	2.46%	2.54%	2.44%
	4	0.00%	2.47%	2.55%	2.49%	2.45%
	5	0.00%	2.35%	2.55%	2.55%	2.45%
	6	0.00%	2.64%	2.45%	2.58%	2.45%
	7	0.00%	2.40%	2.34%	2.59%	2.48%
	8	0.00%	2.51%	2.29%	2.63%	2.51%
	9	0.00%	2.37%	2.04%	2.58%	2.47%
	10	0.00%	2.50%	1.06%	2.64%	2.51%
0.45	2	0.21%	2.33%	2.41%	2.51%	2.41%
	3	0.03%	2.44%	2.53%	2.59%	2.50%
	4	0.01%	2.30%	2.58%	2.53%	2.47%
	5	0.00%	2.30%	2.47%	2.58%	2.50%
	6	0.00%	2.36%	2.57%	2.64%	2.46%
	7	0.00%	2.25%	2.58%	2.59%	2.48%
	8	0.00%	2.35%	2.57%	2.46%	2.47%
	9	0.00%	2.27%	2.60%	2.58%	2.44%
	10	0.00%	2.32%	2.56%	2.48%	2.51%
0.9	2	0.84%	2.19%	2.54%	2.65%	2.52%
	3	0.45%	1.94%	2.56%	2.53%	2.54%
	4	0.25%	1.80%	2.55%	2.59%	2.52%
	5	0.21%	1.62%	2.44%	2.44%	2.44%
	6	0.17%	1.72%	2.47%	2.71%	2.56%
	7	0.12%	1.55%	2.45%	2.50%	2.50%
	8	0.11%	1.54%	2.43%	2.49%	2.47%
	9	0.10%	1.41%	2.47%	2.56%	2.50%
	10	0.09%	1.50%	2.49%	2.52%	2.58%

Table S3. Power in the simulation with two to ten components and treatment effects of 10%

Correlation	Number of components	Co-primary	Multiple primary	Composite[all]	Composite[≥K/2]	Net benefit
A) Marginal proportions in the control arm: 20%						
0	2	40.8%	77.8%	53.8%	85.8%	88.2%
	3	26.3%	85.1%	28.6%	87.4%	88.1%
	4	16.6%	89.2%	5.9%	97.1%	88.1%
	5	10.7%	91.9%	0.2%	93.3%	88.4%
	6	6.8%	93.7%	0.0%	98.8%	88.1%
	7	4.4%	95.2%	0.0%	94.8%	88.1%
	8	2.7%	96.3%	0.0%	99.2%	88.2%
	9	1.8%	96.8%	0.0%	94.6%	88.0%
	10	1.2%	97.6%	0.0%	99.1%	88.2%
0.45	2	44.8%	73.6%	57.1%	78.3%	81.7%
	3	33.3%	78.4%	48.0%	76.6%	81.5%
	4	25.7%	81.0%	39.6%	84.1%	81.6%
	5	20.5%	82.8%	33.7%	80.3%	81.4%
	6	17.1%	84.2%	28.0%	85.8%	81.8%
	7	14.2%	85.0%	23.7%	82.3%	81.6%
	8	11.9%	86.1%	20.6%	86.3%	81.4%
	9	10.4%	86.6%	18.8%	83.4%	81.4%
	10	8.9%	87.5%	16.4%	86.6%	81.4%
0.9	2	51.9%	65.4%	60.7%	69.0%	71.1%
	3	45.5%	66.3%	58.7%	66.2%	71.2%
	4	41.2%	66.3%	57.0%	68.9%	71.3%
	5	37.9%	65.8%	55.3%	67.0%	71.2%
	6	35.5%	65.9%	54.3%	68.6%	71.3%
	7	33.3%	65.4%	53.0%	66.9%	70.8%
	8	31.7%	65.9%	52.2%	68.4%	71.1%
	9	30.6%	65.3%	51.4%	67.4%	71.1%
	10	29.1%	65.4%	51.0%	68.4%	71.1%
B) Marginal proportions in the control arm: 60%						
0	2	31.3%	69.3%	75.2%	57.0%	80.8%
	3	17.2%	76.6%	81.5%	86.2%	80.5%
	4	9.7%	81.6%	82.2%	82.0%	80.6%
	5	5.5%	85.0%	79.8%	95.6%	80.5%
	6	3.0%	87.5%	75.5%	92.1%	80.6%
	7	1.7%	90.0%	68.2%	98.5%	80.9%
	8	1.0%	91.3%	60.3%	96.3%	80.7%
	9	0.5%	92.5%	49.3%	99.4%	80.7%
	10	0.3%	93.5%	39.5%	98.0%	80.5%
0.45	2	35.8%	64.2%	66.4%	54.9%	72.6%
	3	24.9%	69.1%	69.5%	70.4%	72.8%
	4	18.3%	72.0%	70.4%	67.9%	72.8%
	5	14.0%	73.7%	69.9%	75.6%	72.6%
	6	11.3%	75.1%	69.2%	73.4%	72.9%
	7	9.0%	76.3%	68.5%	78.2%	72.8%
	8	7.4%	77.6%	67.4%	76.6%	72.8%
	9	6.3%	78.4%	66.1%	79.9%	73.0%
	10	5.3%	79.1%	65.0%	78.0%	72.7%
0.9	2	43.7%	56.8%	58.4%	54.7%	62.3%
	3	37.0%	57.1%	59.5%	58.4%	62.2%
	4	33.0%	56.9%	60.4%	57.3%	62.2%
	5	30.0%	56.7%	60.8%	59.1%	62.1%
	6	27.8%	56.2%	60.9%	58.2%	62.2%
	7	26.2%	56.1%	61.0%	59.3%	62.0%
	8	24.6%	56.0%	60.9%	58.7%	62.2%
	9	23.5%	55.8%	61.0%	59.5%	62.1%
	10	22.2%	55.5%	60.9%	59.0%	62.1%

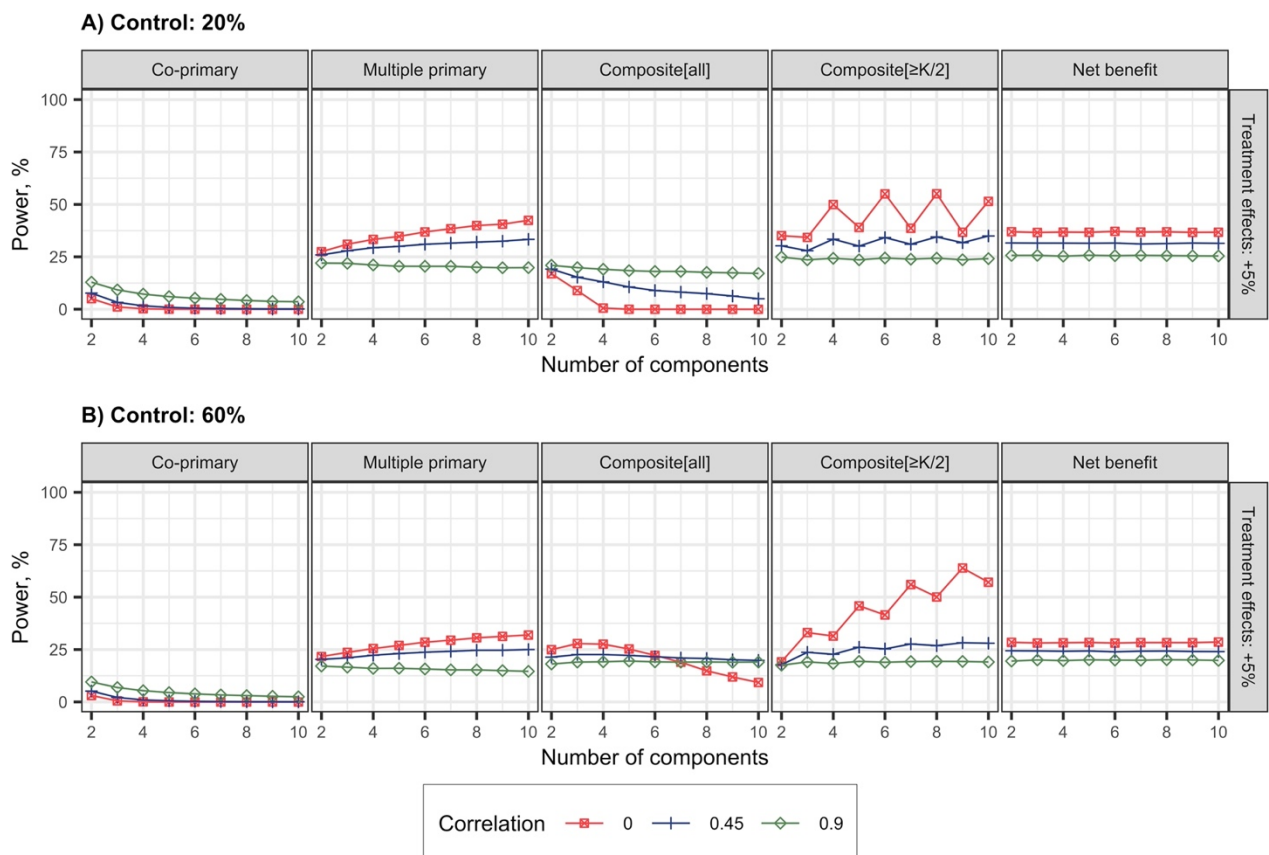


Figure S1. Power in the simulation with two to ten components and treatment effects of 5% according to the marginal proportions in the control arm (A 20%; B 60%)

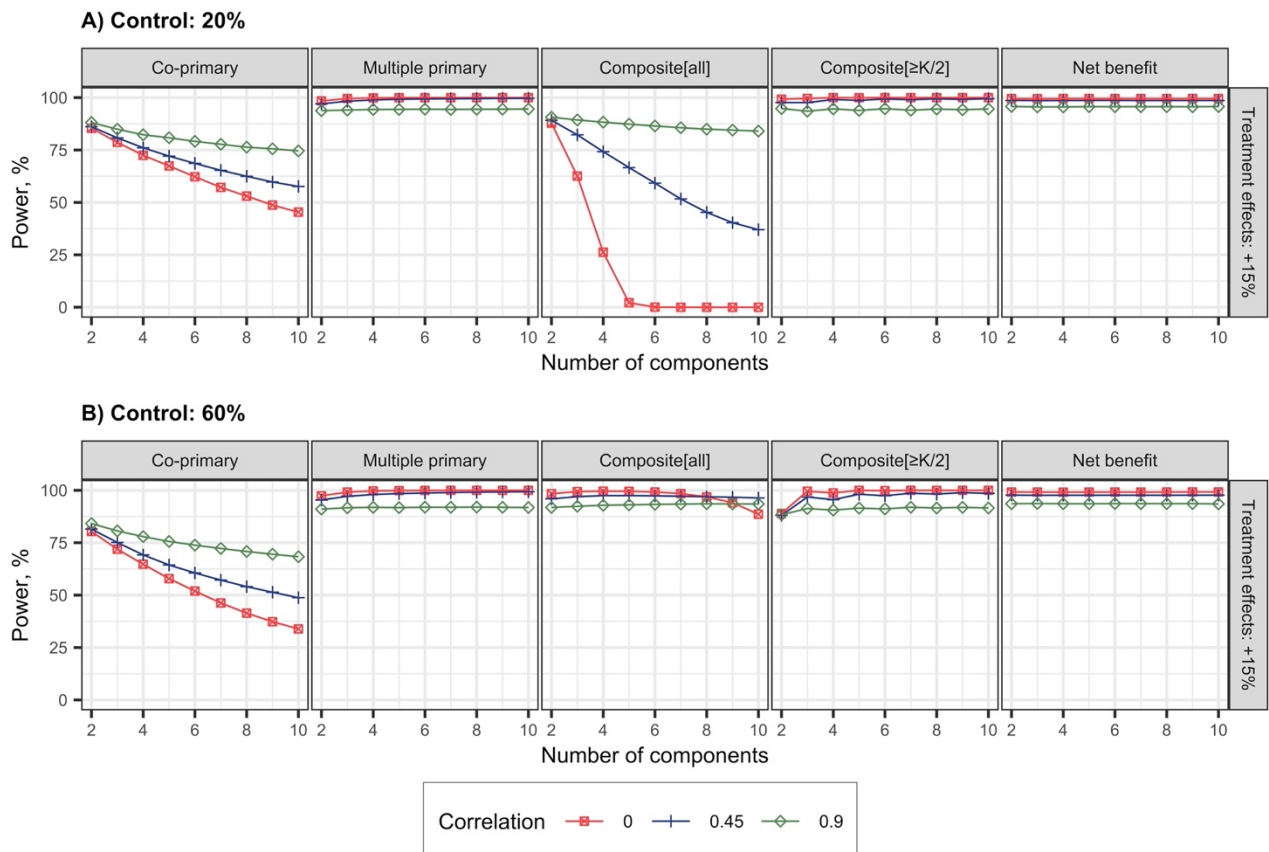


Figure S2. Power in the simulation with two to ten components and treatment effects of 15% according to the marginal proportions in the control arm (A 20%; B 60%)

Table S4. Power in the simulation with two components and $\rho_e = \rho_c$

Treatment effects	Correlation	Component 1	Component 2	Co-primary	Multiple primary	Composite[all]	Composite[≥ 1]	Net benefit
A) Marginal proportions in the control arm: 20% and 40%								
+10%, +10%	-0.9	64.5%	51.9%	25.8%	80.0%	14.3%	98.7%	98.0%
	-0.45	64.0%	52.0%	29.3%	75.7%	61.2%	87.5%	92.1%
	0	64.6%	52.0%	33.5%	72.0%	60.2%	75.2%	85.0%
	0.45	64.3%	52.2%	37.7%	67.7%	59.4%	65.8%	76.7%
	0.9	64.5%	52.1%	43.0%	62.2%	62.4%	54.9%	65.9%
+10%, 0%	-0.9	64.3%	2.4%	0.5%	53.9%	0.3%	53.8%	72.5%
	-0.45	64.4%	2.5%	1.0%	53.8%	23.8%	32.3%	57.8%
	0	64.2%	2.5%	1.6%	53.4%	26.8%	22.5%	45.6%
	0.45	64.3%	2.6%	2.2%	53.1%	30.5%	15.9%	33.6%
	0.9	64.3%	2.5%	2.5%	53.0%	46.8%	6.2%	18.1%
0%, 0%	-0.9	2.5%	2.5%	0.0%	2.5%	0.0%	2.6%	2.6%
	-0.45	2.5%	2.4%	0.0%	2.5%	2.5%	2.4%	2.5%
	0	2.6%	2.5%	0.1%	2.5%	2.5%	2.5%	2.4%
	0.45	2.5%	2.6%	0.2%	2.5%	2.6%	2.6%	2.5%
	0.9	2.6%	2.6%	0.6%	2.4%	2.6%	2.5%	2.6%
+15%, -5%	-0.9	92.4%	0.1%	0.1%	87.2%	0.4%	53.5%	87.5%
	-0.45	92.6%	0.2%	0.1%	87.4%	25.4%	31.1%	74.8%
	0	92.4%	0.1%	0.1%	87.3%	29.4%	20.9%	60.0%
	0.45	92.5%	0.2%	0.2%	87.3%	34.0%	14.0%	43.8%
	0.9	92.5%	0.1%	0.1%	87.3%	56.9%	3.9%	20.2%
-5%, +15%	-0.9	0.1%	85.6%	0.0%	77.5%	0.0%	55.6%	15.1%
	-0.45	0.1%	85.6%	0.0%	77.6%	5.1%	49.2%	15.1%
	0	0.1%	85.7%	0.0%	77.5%	3.1%	50.2%	18.0%
	0.45	0.1%	85.6%	0.1%	77.6%	1.3%	59.3%	24.8%
	0.9	0.1%	85.6%	0.1%	77.7%	0.1%	82.3%	43.3%
B) Marginal proportions in the control arm: 60% and 40%								
+10%, +10%	-0.9	56.0%	52.2%	18.1%	77.2%	98.7%	90.5%	96.1%
	-0.45	56.3%	52.2%	24.8%	71.3%	80.3%	71.7%	87.6%
	0	56.2%	52.0%	29.3%	66.6%	67.9%	63.0%	79.8%
	0.45	56.3%	52.1%	33.8%	62.3%	60.6%	58.1%	71.9%
	0.9	56.3%	52.4%	39.8%	56.7%	53.5%	55.6%	63.0%
+10%, 0%	-0.9	56.2%	2.5%	0.1%	45.7%	50.9%	49.4%	76.5%
	-0.45	56.4%	2.5%	0.7%	45.5%	21.8%	33.9%	56.7%
	0	56.2%	2.4%	1.4%	45.1%	14.9%	31.5%	44.1%
	0.45	56.4%	2.4%	1.9%	45.0%	10.1%	34.1%	33.5%
	0.9	56.0%	2.5%	2.4%	44.2%	3.7%	49.1%	21.6%
0%, 0%	-0.9	2.5%	2.5%	0.0%	2.5%	2.5%	2.6%	2.6%
	-0.45	2.5%	2.4%	0.0%	2.5%	2.5%	2.6%	2.5%
	0	2.5%	2.5%	0.1%	2.5%	2.5%	2.5%	2.4%
	0.45	2.4%	2.5%	0.2%	2.3%	2.5%	2.5%	2.4%
	0.9	2.5%	2.5%	0.6%	2.2%	2.6%	2.6%	2.5%
+15%, -5%	-0.9	89.9%	0.2%	0.0%	83.7%	46.8%	58.1%	94.6%
	-0.45	89.9%	0.1%	0.1%	83.8%	14.9%	47.0%	77.8%
	0	89.9%	0.1%	0.1%	83.6%	7.7%	49.4%	60.6%
	0.45	89.9%	0.1%	0.1%	83.8%	3.2%	59.4%	43.0%
	0.9	89.8%	0.1%	0.1%	83.5%	0.3%	85.2%	22.2%
-5%, +15%	-0.9	0.1%	85.7%	0.0%	77.8%	56.2%	39.1%	3.7%
	-0.45	0.1%	85.7%	0.1%	77.9%	32.9%	20.1%	5.2%
	0	0.1%	85.7%	0.1%	77.7%	29.2%	14.6%	6.9%
	0.45	0.2%	85.5%	0.2%	77.5%	29.9%	10.8%	8.9%
	0.9	0.2%	85.5%	0.2%	77.5%	44.4%	3.9%	13.7%

Table S5. Sample size per arm to achieve 90% power with reduced treatment effects: **Pain-free** (27.9% [3.8 mg], 14.3% [*placebo*]); **MBS-free** (55.6%, 42.9%)

Method	Correlation in the control arm	Correlation in the experimental arm				
		-0.9	-0.45	0	0.45	0.9
Co-primary	-0.9	335	336	336	335	335
	-0.45	336	336	335	336	333
	0	336	335	335	335	333
	0.45	336	335	335	335	335
	0.9	335	335	335	334	333
Multiple primary	-0.9	135	143	153	162	170
	-0.45	138	150	156	166	172
	0	143	154	165	171	182
	0.45	152	164	171	181	188
	0.9	158	168	180	186	197
Composite[all]	-0.9	497	71	42	30	23
	-0.45	> 9999	224	87	48	33
	0	> 9999	1496	221	98	58
	0.45	> 9999	> 9999	853	217	103
	0.9	> 9999	> 9999	> 9999	571	190
Composite[≥1]	-0.9	69	161	418	2179	> 9999
	-0.45	58	125	284	992	> 9999
	0	47	89	174	430	2163
	0.45	36	64	113	224	631
	0.9	31	50	82	144	312
Net benefit	-0.9	67	105	163	275	556
	-0.45	64	97	146	238	455
	0	59	86	124	193	337
	0.45	55	77	107	157	256
	0.9	51	70	93	131	203

Bold Italic: results with the same correlation values for both arms

Table S6. Sample size per arm to achieve 90% power with reduced treatment effects: **Pain-free** (27.9% [3.8 mg], 14.3% [*placebo*]); **MBS-free** (55.6%, 42.9%); **no TEAEs** (69.7%, 81.9%)

Method	Correlation		
	0	0.45	0.9
Co-primary	> 9999	> 9999	> 9999
Multiple primary	181	198	215
Composite[all]	443	916	1651
Composite[≥2]	620	434	346
Net benefit	125	156	203

Table S7. Sample size per arm to achieve 90% power in additional correlation scenarios: **Pain-free** (41.5% [3.8 mg], 14.3% [*placebo*]); **MBS-free** (68.3%, 42.9%); **no TEAEs** (57.5%, 81.9%)

Method	Correlation*	
	0.45	0.9
Co-primary	> 9999	> 9999
Multiple primary	56	61
Composite[all]	105	61
Composite[≥2]	283	282
Net benefit	42	52

*Correlation between pain freedom, MBS freedom, and the *absence* of TEAEs