# Sample Size Estimation using a Latent Variable Model for Mixed Outcome Co-Primary, Multiple Primary and Composite Endpoints: Supplementary Material

## 1. Composite endpoints

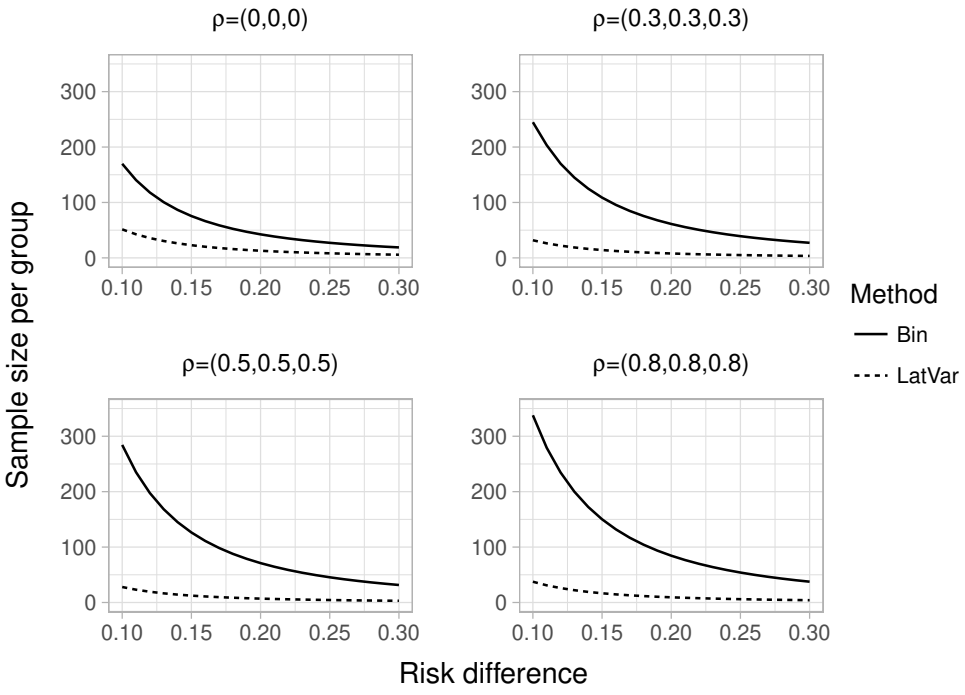


Fig. 1. Estimated sample size per group for different values of the risk difference using the latent variable and standard binary methods when the composite endpoint is formed from one continuous, one ordinal and one binary outcome, where all components drive response and correlations between the outcomes are between 0 and 0.8, where $\rho = (\rho_{12}, \rho_{13}, \rho_{23})$

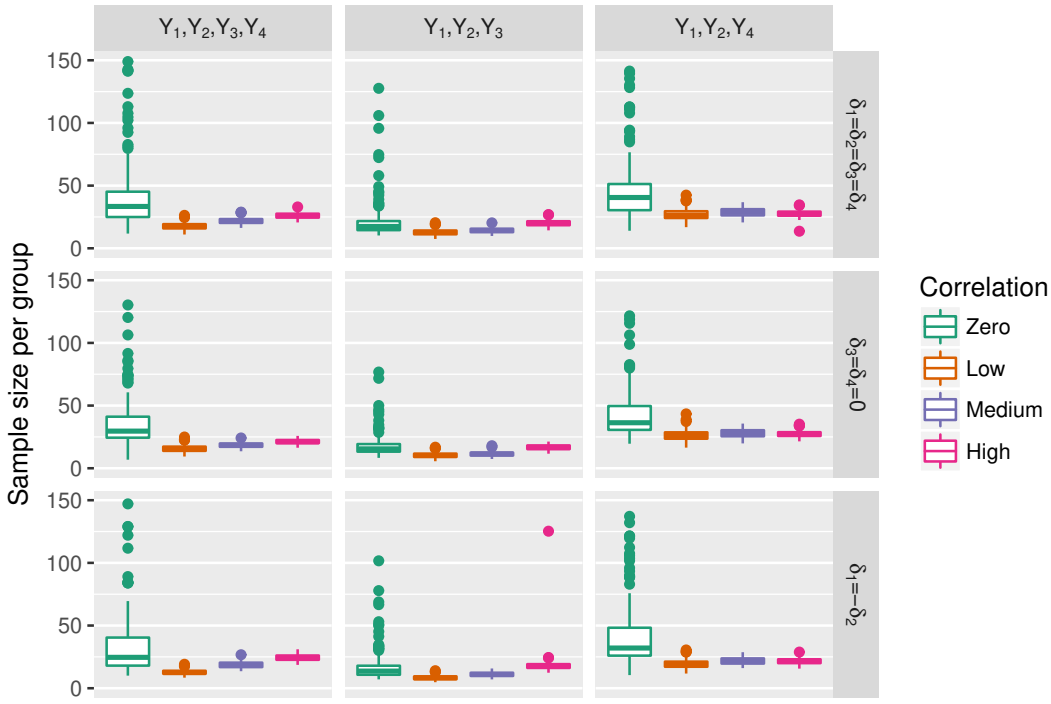


Fig. 2. Boxplots of the estimated sample size per group from 1000 simulated datasets using the latent variable method for composites containing two continuous, one ordinal and one binary component and correlation between endpoints is zero, low=0.3, medium=0.5 or high=0.8. These are shown when response is driven by $(Y_1, Y_2, Y_3, Y_4)$, $(Y_1, Y_2, Y_3)$ or $(Y_1, Y_2, Y_4)$ and the treatment effect structure in the components is $\delta_1 = \delta_2 = \delta_3 = \delta_4$, $\delta_3 = \delta_4 = 0$ or $\delta_1 = -\delta_2$

Table 1. Median sample sizes $n = n_C = n_T$ for overall power $1 - \beta \approx 80\%$, $\alpha = 0.05$, $k_m = 1, K = 3$, $\delta = \mu_T - \mu_C$ : overall risk difference on the composite, $\delta^\dagger$ : treatment effect structure in the components, for a combination of correlations 0, L=0.3, M=0.5, H=0.8 using the latent variable model when the composite is made up of one continuous, one ordinal and one binary outcome

| Response | $\delta^\dagger$ | $\delta$ | Correlation $(\rho_{12}, \rho_{13}, \rho_{23})$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 000 | 00H | LLL | LLH | MMM | MMH | HHH |
| $Y_1, Y_2, Y_3$ | $\delta_1 = \delta_2 = \delta_3$ | 0.05 | 206 | 339 | 128 | 119 | 112 | 108 | 145 |
| | | 0.10 | 52 | 85 | 32 | 30 | 28 | 27 | 38 |
| | | 0.15 | 23 | 38 | 15 | 14 | 13 | 12 | 17 |
| | $\delta_3 = 0$ | 0.05 | 201 | 334 | 123 | 117 | 105 | 112 | 159 |
| | | 0.10 | 51 | 84 | 31 | 30 | 27 | 28 | 40 |
| | | 0.15 | 23 | 38 | 14 | 13 | 12 | 13 | 18 |
| | $\delta_2 = \delta_3 = 0$ | 0.05 | 197 | 329 | 119 | 114 | 101 | 106 | 121 |
| | | 0.10 | 49 | 81 | 29 | 29 | 27 | 21 | 30 |
| | | 0.15 | 21 | 36 | 14 | 13 | 12 | 12 | 15 |
| $Y_1, Y_3$ | $\delta_1 = \delta_2 = \delta_3$ | 0.05 | 474 | 494 | 289 | 200 | 267 | 205 | 240 |
| | | 0.10 | 119 | 124 | 73 | 50 | 67 | 52 | 60 |
| | | 0.15 | 53 | 55 | 33 | 23 | 30 | 23 | 27 |
| | $\delta_3 = 0$ | 0.05 | 468 | 499 | 286 | 195 | 264 | 203 | 248 |
| | | 0.10 | 117 | 125 | 72 | 49 | 66 | 51 | 62 |
| | | 0.15 | 52 | 56 | 32 | 22 | 30 | 23 | 28 |
| | $\delta_2 = \delta_3 = 0$ | 0.05 | 470 | 501 | 287 | 196 | 264 | 204 | 249 |
| | | 0.10 | 119 | 123 | 73 | 49 | 67 | 51 | 63 |
| | | 0.15 | 53 | 55 | 32 | 23 | 31 | 24 | 28 |
| $Y_3$ | $\delta_1 = \delta_2 = \delta_3$ | 0.05 | 1493 | 1472 | 1250 | 1113 | 948 | 793 | 609 |
| | | 0.10 | 374 | 368 | 313 | 279 | 237 | 199 | 153 |
| | | 0.15 | 166 | 164 | 139 | 124 | 106 | 89 | 68 |
| | $\delta_3 = 0$ | 0.05 | 1502 | 1468 | 1256 | 1113 | 960 | 806 | 622 |
| | | 0.10 | 376 | 367 | 315 | 279 | 240 | 202 | 156 |
| | | 0.15 | 176 | 164 | 140 | 124 | 107 | 90 | 70 |
| | $\delta_2 = \delta_3 = 0$ | 0.05 | 1504 | 1465 | 1259 | 1115 | 963 | 807 | 624 |
| | | 0.10 | 376 | 370 | 316 | 280 | 241 | 203 | 156 |
| | | 0.15 | 174 | 164 | 139 | 126 | 106 | 90 | 70 |

Table 2. Median sample sizes $n = n_C = n_T$ for overall power $1 - \beta \approx 80\%$, $\alpha = 0.05$, $k_m = 1, K = 3$, $\delta = \mu_T - \mu_C$ : overall risk difference on the composite, $\delta^\dagger$ : treatment effect structure in the components, for a combination of correlations ranging from 0, L=0.3, M=0.5, H=0.8 using the standard binary method when the composite is made up of one continuous, one ordinal and one binary outcome

| Response | $\delta^\dagger$ | $\delta$ | Correlation $(\rho_{12}, \rho_{13}, \rho_{23})$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 000 | 00H | LLL | LLH | MMM | MMH | HHH |
| $Y_1, Y_2, Y_3$ | $\delta_1 = \delta_2 = \delta_3$ | 0.05 | 680 | 965 | 980 | 1141 | 1138 | 1214 | 1352 |
| | | 0.10 | 170 | 242 | 245 | 286 | 285 | 304 | 338 |
| | | 0.15 | 76 | 108 | 109 | 127 | 127 | 135 | 151 |
| | $\delta_3 = 0$ | 0.05 | 628 | 939 | 928 | 1098 | 1102 | 1183 | 1332 |
| | | 0.10 | 157 | 235 | 232 | 275 | 276 | 296 | 333 |
| | | 0.15 | 70 | 105 | 104 | 122 | 123 | 132 | 148 |
| | $\delta_2 = \delta_3 = 0$ | 0.05 | 609 | 920 | 914 | 1086 | 1097 | 1171 | 1310 |
| | | 0.10 | 147 | 231 | 228 | 270 | 271 | 290 | 328 |
| | | 0.15 | 68 | 101 | 101 | 119 | 121 | 130 | 146 |
| $Y_1, Y_3$ | $\delta_1 = \delta_2 = \delta_3$ | 0.05 | 1127 | 1136 | 1255 | 1261 | 1334 | 1320 | 1425 |
| | | 0.10 | 282 | 284 | 314 | 316 | 334 | 330 | 357 |
| | | 0.15 | 126 | 127 | 140 | 141 | 149 | 147 | 159 |
| | $\delta_3 = 0$ | 0.05 | 1078 | 1072 | 1216 | 1218 | 1298 | 1296 | 1403 |
| | | 0.10 | 270 | 268 | 304 | 305 | 325 | 324 | 351 |
| | | 0.15 | 120 | 120 | 136 | 136 | 145 | 144 | 156 |
| | $\delta_2 = \delta_3 = 0$ | 0.05 | 1066 | 1063 | 1202 | 1209 | 1296 | 1297 | 1403 |
| | | 0.10 | 263 | 259 | 300 | 299 | 319 | 324 | 351 |
| | | 0.15 | 121 | 119 | 133 | 131 | 143 | 143 | 156 |
| $Y_3$ | $\delta_1 = \delta_2 = \delta_3$ | 0.05 | 1547 | 1548 | 1550 | 1548 | 1550 | 1550 | 1549 |
| | | 0.10 | 387 | 387 | 388 | 387 | 388 | 388 | 388 |
| | | 0.15 | 172 | 172 | 173 | 172 | 173 | 173 | 173 |
| | $\delta_3 = 0$ | 0.05 | 1544 | 1545 | 1549 | 1548 | 1549 | 1548 | 1545 |
| | | 0.10 | 386 | 387 | 388 | 387 | 388 | 387 | 387 |
| | | 0.15 | 172 | 172 | 173 | 172 | 173 | 172 | 172 |
| | $\delta_2 = \delta_3 = 0$ | 0.05 | 1544 | 1546 | 1549 | 1546 | 1551 | 1549 | 1545 |
| | | 0.10 | 386 | 389 | 387 | 385 | 388 | 388 | 387 |
| | | 0.15 | 173 | 172 | 173 | 173 | 172 | 172 | 172 |

Table 3. Median sample sizes per group $n = n_C = n_T$ for overall power $1 - \beta \approx 80\%$, $\alpha = 0.05$, $k_m = 2, K = 4$, $\delta = \mu_T - \mu_C$ : overall risk difference on the composite , $\delta^\dagger$: treatment effect structure in the components, for a combination of correlations 0, L=0.3, M=0.5, H=0.8 using the latent variable model when the composite is comprised of two continuous, one ordinal and one binary outcome

| Response | $\delta^\dagger$ | $\delta$ | Correlation $(\rho_{12}, \rho_{13}, \rho_{14}, \rho_{23}, \rho_{24}, \rho_{34})$ | | | |
|---|---|---|---|---|---|---|
| | | | 000000 | LLLLLL | MMMMMM | HHHHHH |
| $Y_1, Y_2, Y_3, Y_4$ | $\delta_1 = \delta_2 = \delta_3 = \delta_4$ | 0.05 | 70 | 51 | 41 | 81 |
| | | 0.10 | 18 | 13 | 11 | 21 |
| | | 0.15 | 8 | 6 | 5 | 9 |
| | $\delta_3 = \delta_4 = 0$ | 0.05 | 62 | 41 | 47 | 67 |
| | | 0.10 | 16 | 11 | 12 | 17 |
| | | 0.15 | 7 | 5 | 6 | 8 |
| | $\delta_1 = -\delta_2$ | 0.05 | 55 | 34 | 45 | 72 |
| | | 0.10 | 14 | 9 | 12 | 18 |
| | | 0.15 | 7 | 4 | 5 | 8 |
| $Y_1, Y_2, Y_3$ | $\delta_1 = \delta_2 = \delta_3 = \delta_4$ | 0.05 | 139 | 71 | 63 | 105 |
| | | 0.10 | 35 | 18 | 16 | 27 |
| | | 0.15 | 16 | 8 | 7 | 12 |
| | $\delta_3 = \delta_4 = 0$ | 0.05 | 120 | 63 | 75 | 85 |
| | | 0.10 | 30 | 16 | 19 | 22 |
| | | 0.15 | 13 | 7 | 9 | 10 |
| | $\delta_1 = -\delta_2$ | 0.05 | 105 | 50 | 76 | 99 |
| | | 0.10 | 27 | 13 | 19 | 25 |
| | | 0.15 | 12 | 6 | 9 | 11 |
| $Y_1, Y_2, Y_4$ | $\delta_1 = \delta_2 = \delta_3 = \delta_4$ | 0.05 | 166 | 106 | 105 | 112 |
| | | 0.10 | 42 | 27 | 27 | 28 |
| | | 0.15 | 19 | 12 | 12 | 13 |
| | $\delta_3 = \delta_4 = 0$ | 0.05 | 147 | 105 | 113 | 111 |
| | | 0.10 | 37 | 27 | 29 | 28 |
| | | 0.15 | 17 | 12 | 13 | 13 |
| | $\delta_1 = -\delta_2$ | 0.05 | 132 | 78 | 88 | 86 |
| | | 0.10 | 33 | 20 | 22 | 22 |
| | | 0.15 | 15 | 9 | 10 | 10 |

Table 4. Median sample sizes per group $n = n_C = n_T$ for overall power $1 - \beta \approx 80\%$, $\alpha = 0.05$, $k_m = 2, K = 4$, $\delta = \mu_T - \mu_C$ : overall risk difference on the composite, $\delta^\dagger$: treatment effect structure in the components, for a combination of correlations 0, L=0.3, M=0.5, H=0.8 using the standard binary method when the composite is comprised of two continuous, one ordinal and one binary outcome

| Response | $\delta^\dagger$ | $\delta$ | Correlation $(\rho_{12}, \rho_{13}, \rho_{14}, \rho_{23}, \rho_{24}, \rho_{34})$ | | | |
|---|---|---|---|---|---|---|
| | | | 000000 | LLLLLL | MMMMMM | HHHHHH |
| $Y_1, Y_2, Y_3, Y_4$ | $\delta_1 = \delta_2 = \delta_3 = \delta_4$ | 0.05 | 386 | 739 | 665 | 1240 |
| | | 0.10 | 97 | 185 | 167 | 310 |
| | | 0.15 | 43 | 83 | 74 | 138 |
| | $\delta_3 = \delta_4 = 0$ | 0.05 | 324 | 665 | 867 | 1205 |
| | | 0.10 | 81 | 167 | 217 | 302 |
| | | 0.15 | 36 | 74 | 97 | 134 |
| | $\delta_1 = -\delta_2$ | 0.05 | 331 | 666 | 858 | 1169 |
| | | 0.10 | 83 | 167 | 215 | 293 |
| | | 0.15 | 37 | 74 | 96 | 130 |
| $Y_1, Y_2, Y_3$ | $\delta_1 = \delta_2 = \delta_3 = \delta_4$ | 0.05 | 690 | 956 | 912 | 1300 |
| | | 0.10 | 173 | 239 | 228 | 325 |
| | | 0.15 | 77 | 107 | 102 | 145 |
| | $\delta_3 = \delta_4 = 0$ | 0.05 | 650 | 912 | 1053 | 1283 |
| | | 0.10 | 163 | 228 | 264 | 321 |
| | | 0.15 | 73 | 102 | 117 | 143 |
| | $\delta_1 = -\delta_2$ | 0.05 | 605 | 866 | 1017 | 1232 |
| | | 0.10 | 152 | 217 | 255 | 308 |
| | | 0.15 | 68 | 97 | 113 | 137 |
| $Y_1, Y_2, Y_4$ | $\delta_1 = \delta_2 = \delta_3 = \delta_4$ | 0.05 | 690 | 962 | 919 | 1298 |
| | | 0.10 | 173 | 241 | 230 | 325 |
| | | 0.15 | 77 | 107 | 103 | 145 |
| | $\delta_3 = \delta_4 = 0$ | 0.05 | 642 | 919 | 1058 | 1281 |
| | | 0.10 | 161 | 230 | 265 | 321 |
| | | 0.15 | 72 | 103 | 118 | 143 |
| | $\delta_1 = -\delta_2$ | 0.05 | 610 | 876 | 1007 | 1225 |
| | | 0.10 | 153 | 219 | 252 | 307 |
| | | 0.15 | 68 | 98 | 112 | 137 |