Supplementary Material to the paper 'Sample size for competing risks survival analysis in fixed and group-sequential designs'

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S.1 Simulation studies under fixed design: Gompertz distribution

Figure S1 shows the statistical power computation for the Gompertz distribution under both the modeling approaches.

The three scenarios with $CIF_{1E} = 0.10, 0.20, 0.30$ are associated with a sample size of about 1100, 600 and 400, respectively, showing again results very similar to those under the exponential and Weibull distributions.

For the Gompertz distribution, in the scenario with adverse type-2 treatment effect ($\theta_2 = 1.2$), the two approaches showed very similar results for sample size calculation, with an advantage of the SDH approach for higher CIF_{1E} and weaker type-1 treatment effect. Indeed, under the Gompertz distribution, in the first scenario when $\theta_2 = 1.2$, with $CIF_{1E} = 0.10$, the SDH approach performs slightly better for $\theta_1 = 0.4$ (275 for SDH and 300 for CSH) and for $\theta_1 = 0.6$, the sample size is about 1000 for the SDH approach and 1150 for the CSH approach. In the third scenario with $CIF_{1E} = 0.30$, when $\theta_1 = 0.8$ the sample size under the SDH approach showed a reduction of more than 200 units, as compared to the size obtained under the CSH approach.

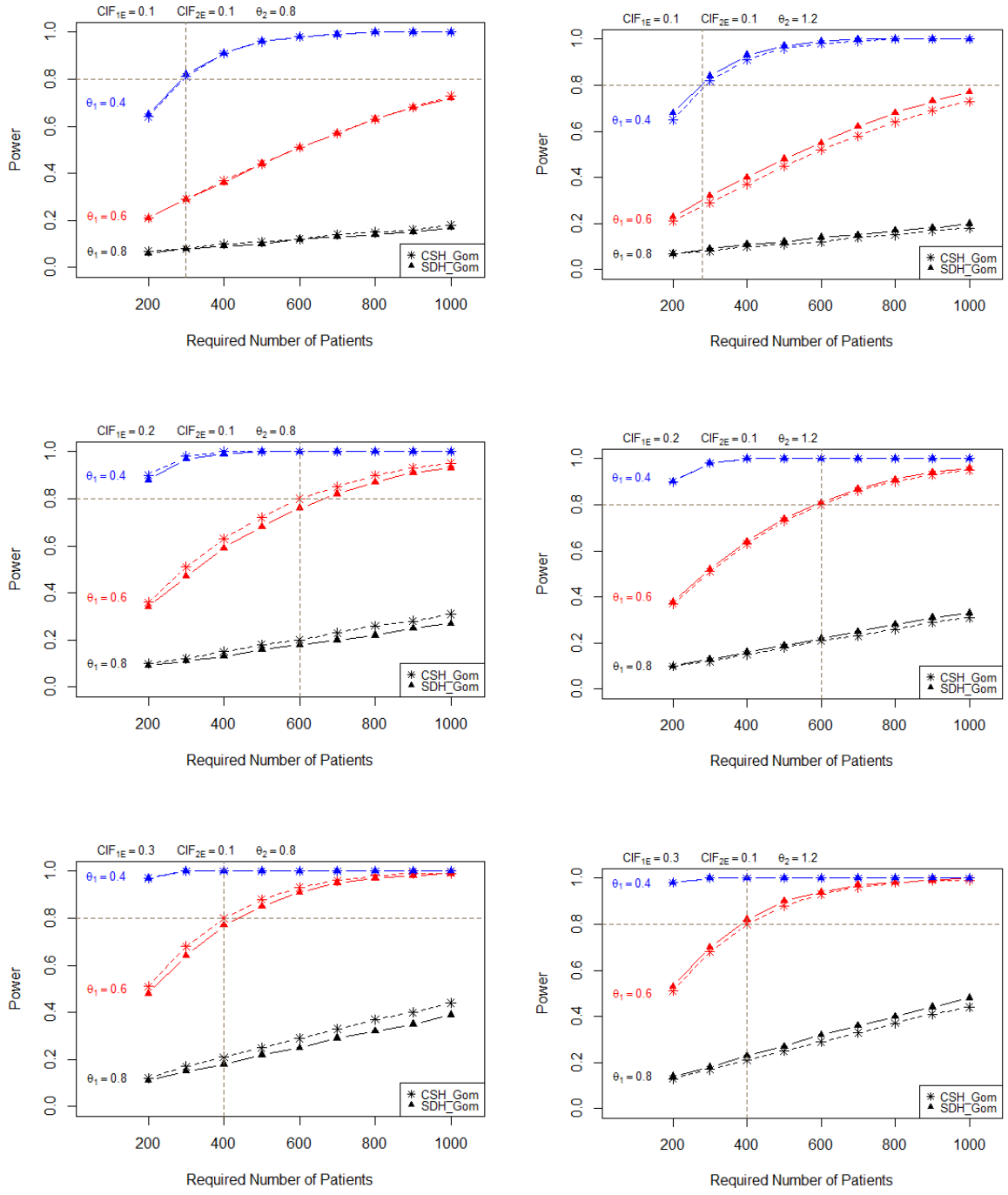


Figure S1: Functional relation between statistical power and sample size under the Gompertz distribution for the CSH and SDH approaches. Results are shown for different values of type-1 cumulative incidence ($CIF_{1E} = 0.1, 0.2, 0.3$), of type-1 positive treatment effect ($\theta_1 = 0.4, 0.6, 0.8$) and of type-1 treatment effect ($\theta_2 = 0.8, 1.2$).

S.2 Simulation studies under fixed design: Different shape parameters

Choosing a specific probabilistic model, such as an exponential, Weibull, or Gompertz time-to-event distribution, also depends on the particular study design. If the study design suggests that the time-to-event follows, e.g., a Weibull distribution, then assuming other distributions that lead to smaller sample sizes would be misleading. However, given a specific time-to-event distribution, it is often of interest to study how sample size behaves when changing the shape parameter values.

For this scope, a simulation study was conducted using the CSH and SDH approaches, where we considered different known values of the shape parameters in the Weibull and Gompertz distributions. Here, it is assumed that $\tilde{\gamma}_{1E} = \tilde{\gamma}_{1C}$ and $\tilde{\eta}_{1E} = \tilde{\eta}_{1C}$, and that $\tilde{\gamma}_{1E} = \gamma^*_{1C} = 0.5, 1.5$ and $\tilde{\eta}_{1E} = \eta^*_{1E} = -0.5, 0.5$ for the Weibull and Gompertz distributions, respectively. Furthermore, the CSH rates λ_{1E} and λ_{2E} for the main and competing events for the experimental group were assumed. Then, for fixed values of θ_1 and θ_2, the control group hazard rates, λ_{1C} and λ_{2C}, were computed using the formula: $\theta_k = \lambda_{kE}/\lambda_{kC}$, for $k = 1, 2$. Finally, CIF_{1E}, CIF_{1C} values were computed at time points $t = \tilde{f}, 0.5a + \tilde{f}, t^*$. For instance, under CSH, the CIFs values for type-1 event at time point $t = t^*$ are

$$\begin{cases} \text{Weibull:} & CIF_{1j}(t^*) = \int_0^{t^*} (\lambda_{1j}\tilde{\gamma}_{1j}u^{\tilde{\gamma}_{1j}-1}) \exp\left[-\left(\lambda_{1j}u^{\tilde{\gamma}_{1j}} + \lambda_{2j}u^{\tilde{\gamma}_{2j}}\right)\right] du \\ \text{Gompertz:} & CIF_{1j}(t^*) = \int_0^{t^*} (\lambda_{1j}e^{\tilde{\eta}_{1j}u}) \exp\left[-\left\{\frac{\lambda_{1j}}{\tilde{\eta}_{1j}}\left(e^{\tilde{\eta}_{1j}u} - 1\right) + \frac{\lambda_{2j}}{\tilde{\eta}_{2j}}\left(e^{\tilde{\eta}_{2j}u} - 1\right)\right\}\right] du \end{cases}$$

In a similar manner, the CIF values were computed at the other time points $t = \tilde{f}, 0.5a + \tilde{f}$.

Under the SDH approach, first we need to compute the SDH ratio θ_1^* from the following

equation:

$$\theta_1^* = \frac{\log\{1 - CIF_{1E}(t^*)\}}{\log\{1 - CIF_{1C}(t^*)\}}. \tag{1}$$

The values of $CIF_{1E}(t^*)$ and $CIF_{1C}(t^*)$ were found using the CSH approach. This is done because here it is necessary to have fixed given values for the shape parameters, and thus, the $CIF_{1E}(t^*)$ and $CIF_{1C}(t^*)$ values are obtained from the exponential distribution in the CSH approach by applying equation (7).

Then, to compute λ_{1j}^*, the following formulas are applied:

$$\begin{cases} \text{Weibull:} & \lambda_{1j}^* = -\log(1 - CIF_{1j}(t^*))/t^{*\gamma_{1j}^*} \\ \text{Gompertz:} & \lambda_{1j}^* = \frac{\eta_{1j}^*[-\log(1-CIF_{1j}(t^*))]}{e^{\eta_{1j}^* t^*} - 1}. \end{cases}$$

For a given value of $CIF_{1j}(t^*)$ and assumed $\gamma_{1j}^* = 0.5, 1.5$, $\eta_{1j}^* = -0.5, 0.5$, we obtained the the values of λ_{1j}^*. Then, we can recompute CIF_{1j} values at other time points using the following formula:

$$\begin{cases} \text{Weibull:} & CIF_{1j}(t) = 1 - e^{-\lambda_{1j}^* t^{\gamma_{1j}^*}} \\ \text{Gompertz:} & CIF_{1j}(t) = 1 - exp\left[- \frac{\lambda_{1j}^*(e^{\eta_{1j}^* t} - 1)}{\eta_{1j}^*} \right]. \end{cases}$$

Finally, with all the CIFs values, $\tilde{\Psi}_{1j}$ can be computed using the CSH approach and Ψ_{1j}^* using the SDH approach following equation (11) in Section 2 of the main paper.

Table S1 summarizes simulation results on sample sizes related to the type-1 event of interest for the two different shape parameter values, in combination with Weibull or Gompertz distributions, $\theta_1 = 0.8, 0.6, 0.4$ and $\theta_2 = 0.8, 1.2$. Furthermore, in scenario (a), the hazard rates for both event types are assumed to be equal ($\lambda_{1E} = \lambda_{2E} = 0.03$); in scenario (b), an increased type-1 hazard rate was assumed, $\lambda_{1E} = 0.10$, while keeping unchanged the type-2 event rate, $\lambda_{2E} = 0.03$.

From Table S1, under the Weibull distribution it is observed that with $\tilde{\gamma}_{1j} = \gamma^*_{1j} = 0.5$ (decreasing hazards), the corresponding CIFs are greater under the SDH approach than under the CSH approach, in both scenarios (a) and (b), and thus the SDH approach requires a smaller sample size. When the shape parameter rises to $\tilde{\gamma}_{1j} = \gamma^*_{1j} = 1.5$ (increasing hazards), the CSH approach requires a lower sample size than the SDH approach, due to the corresponding CIFs being higher. Very similar conclusions are observed for the Gompertz distribution.

In scenario (a), when the shape parameters $\tilde{\gamma}$ increased from 0.5 to 1.5, and $\tilde{\eta}$ increased from -0.5 to 0.5, under the CSH approach the sample size reduced by nearly one-third and by more than one-third under the Weibull and Gompertz distributions, respectively. On the contrary, under the SDH approach the sample sizes had an increase of about 30% and even more, respectively for the Weibull and Gompertz distributions. These results are due to the fact that the CIF_{1E} under the CSH approach depends on both cause-1 and cause-2 hazards and it is modified accordingly, whereas the CIF_{1E} under the SDH approach only depends on the subdistribution cause-1 hazard.

The scenario (b) that assumes a higher type-1 event rate for the treatment group (E) is associated with a decreased sample size compared to scenario (a). However, the results and conclusions on the sample size when the shape parameter increases are very similar to those under scenario (a). Moreover, for both scenarios, under the CSH approach, the sample size decreases substantially when we reduce the type-1 hazard rate θ_1, while it is approximately stable, with negligible changes, when the type-2 hazard rate θ_2 rises from 0.8 to 1.2. Contrarily, the SDH approach shows a dependence between the values of the two hazard ratios in determining the sample size. Indeed, when the type-2 hazard rate θ_2 rises from 0.8 to 1.2, a stronger reduction in sample size (about 30%) is observed for $\theta_1 = 0.8$ while a weaker reduction is associated with $\theta_1 \leq 0.6$ (about 10%).

CSH approach						SDH approach				
		Weibull		Gompertz			Weibull		Gompertz	
		$\tilde{\gamma}_{1E}=0.5$	$\tilde{\gamma}_{1E}=1.5$	$\tilde{\eta}_{1E}=-0.5$	$\tilde{\eta}_{1E}=0.5$	θ_1^*	$\gamma_{1E}^*=0.5$	$\gamma_{1E}^*=1.5$	$\eta_{1E}^*=-0.5$	$\eta_{1E}^*=0.5$
Scenario (a):										
		$\lambda_{1E}=\lambda_{2E}=0.03$				λ_{1E}^*:	0.06	0.02	0.07	0.01
CIF_{1E}:		0.06	0.19	0.05	0.27	CIF_{1E}:	0.11	0.11	0.11	0.11
θ_1	θ_2	$\tilde{N}_1$	$\tilde{N}_1$	$\tilde{N}_1$	$\tilde{N}_1$	θ_1^*	N_1^*	N_1^*	N_1^*	N_1^*
0.8	0.8	11495	4272	12827	3319	0.81	7124	9230	6929	10538
0.8	1.2	11427	4196	12760	3238	0.79	5568	7213	5416	8235
0.6	0.8	1865	703	2079	551	0.61	1075	1389	1046	1585
0.6	1.2	1852	690	2067	536	0.60	956	1235	930	1409
0.4	0.8	449	175	500	140	0.41	257	330	250	376
0.4	1.2	446	171	497	136	0.40	238	306	232	348
Scenario (b):										
		$\lambda_{1E}=0.10$		$\lambda_{2E}=0.03$		λ_{1E}^*:	0.19	0.05	0.22	0.03
CIF_{1E}:		0.18	0.50	0.15	0.62	CIF_{1E}:	0.31	0.31	0.31	0.31
θ_1	θ_2	$\tilde{N}_1$	$\tilde{N}_1$	$\tilde{N}_1$	$\tilde{N}_1$	θ_1^*	N_1^*	N_1^*	N_1^*	N_1^*
0.8	0.8	3688	1562	4085	1300	0.82	2517	3189	2456	3611
0.8	1.2	3667	1538	4065	1274	0.79	1912	2422	1866	2742
0.6	0.8	607	268	671	226	0.62	389	490	380	553
0.6	1.2	604	263	668	222	0.60	340	428	332	483
0.4	0.8	152	72	167	63	0.41	99	123	97	138
0.4	1.2	151	71	166	62	0.40	91	113	89	126

Table S1: Required sample size related to the type-1 event of interest for Weibull and Gompertz distributions under the CSH and SDH approaches, with different assumed values for the shape parameter. Here, $a=2$, $\tilde{f}=2$, $CIF_{1E} \equiv CIF_{1E}(t^*)$, $\alpha=0.05$ and $\beta=0.20$.

S.3 Group sequential design: Proof on Fisher Information

Under the assumption of equal size for the two experimental groups, i.e., $p_E = p_C = 1/2$, in the fixed design the Fisher's information $\mathscr{I}$ for $\hat{\beta}_1$ can be written in terms of the number of observed events, $\mathscr{I} = D_1/4$ (Jennison & Turnbull, 2000, Group sequential methods with applications to clinical trials. Chapman and Hall/CRC).

Proof:

Given $\beta = \log\theta$, consider the one-sided test of hypotheses: $H_0 : \beta = 0$ against $H_1 : \beta < 0$. Conclusions will be specular for the alternative $H_1 : \beta > 0$ and for a two-sided test with $H_1 : \beta \neq 0$.

Step (1):

$$\alpha = P(\text{ reject } H_0 \mid H_0) = P\left(\hat{\beta} < -c_\alpha \mid H_0\right) = P\left(\frac{\hat{\beta}-\beta}{\sqrt{Var(\hat{\beta})}} < \frac{-c_\alpha-\beta}{\sqrt{Var(\hat{\beta})}} \mid H_0\right)$$
$$= P\left(Z < \frac{-c_\alpha}{\sqrt{1/\mathscr{I}}}\right) = 1 - \Phi\left(c_\alpha\sqrt{\mathscr{I}}\right)$$

where c_α is the $(1-\alpha)$ critical value. Then, $1-\alpha = \Phi\left(c_\alpha\sqrt{\mathscr{I}}\right)$ and $\Phi^{-1}(1-\alpha) = c_\alpha\sqrt{\mathscr{I}}$. Therefore, $c_\alpha = \Phi^{-1}(1-\alpha)/\sqrt{\mathscr{I}}$.

Step (2):

$$\tilde{\beta} = P(\text{ accept } H_0 \mid H_1) = P\left(\hat{\beta} > -c_\alpha \mid H_1\right) = P\left(\frac{\hat{\beta}-\beta}{\sqrt{Var(\hat{\beta})}} > \frac{-c_\alpha-\beta}{\sqrt{Var(\hat{\beta})}} \mid H_1\right)$$
$$= P\left(Z > \frac{-c_\alpha-\beta}{\sqrt{1/\mathscr{I}}}\right) = 1 - \Phi\left(-(c_\alpha+\beta)\sqrt{\mathscr{I}}\right).$$

Then $\Phi^{-1}(1-\tilde{\beta}) = -c_\alpha\sqrt{\mathscr{I}} - \beta\sqrt{\mathscr{I}}$.

Therefore, replacing c_α with the result from Step (1), we obtain $\Phi^{-1}(1-\tilde{\beta}) = -\Phi^{-1}(1-$

$\alpha) - \beta\sqrt{\mathscr{I}}$. Solving this equation for $\mathscr{I}$, we have that

$$\mathscr{I} = \left[\frac{\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\tilde{\beta})}{\beta}\right]^2 \tag{2}$$

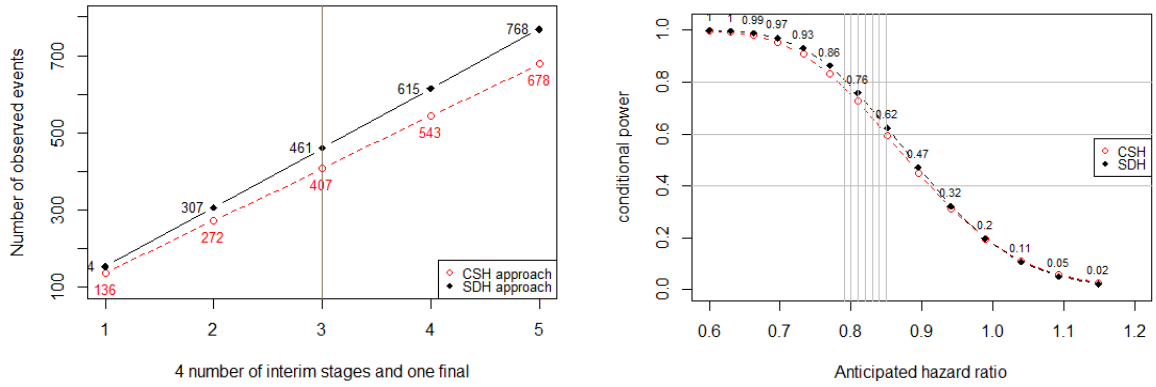
Now recalling formula in equation (2) of Section 2 in the main paper, and given that $p_E = p_C = 1/2$, the required number of events is $D = \left[\frac{\Phi^{-1}(1-\alpha)+\Phi^{-1}(1-\tilde{\beta})}{\beta}\right]^2 \frac{1}{p_E\ p_C} = \frac{\mathscr{I}}{p_E\ p_C} = 4\mathscr{I}$. This implies that $\mathscr{I} = D/4$ and therefore, in fixed design the Fisher information is a function of the size of the number of events.

S.4 Simulation studies under GS design: Conditional power

The conditional power and event sizes are compared for the two competing risks methods. Results are depicted in Figure S2 for the CSH approach (red dashed lines) and the SDH approach (black lines). The information $\mathscr{I}$ was computed using equation (2) in the online Supplementary Material; for the CSH approach we obtained $\mathscr{I} = [(1.97 + 0.84)/\log 0.8]^2 = 158$. Then, the resulting fixed-design event size was $\tilde{D}_1 = 158*4 = 632$. To compute the information $\mathscr{I}_5$ at final stage under the GS design, the inflation factor `IF`= 1.072 was obtained from Table 2.10 in Jennison & Turnbull (2000, Group sequential methods with applications to clinical trials, Chapman and Hall/CRC) thus the result was $\mathscr{I}_5 = 158 * 1.072 = 169$. Then, the information for each interim stage was computed and in particular, for interim stage 3 we obtained $\mathscr{I}_3 = (3/5) * 169 = 101.63$. Thus, the event size was $\tilde{D}_3 = 101.63 * 4 = 407$.

When using the SDH approach, for $\theta_1 = 0.8$ we obtained the SDH ratio $\theta_1^* = 0.81$, and the information was $\mathscr{I} = [(1.97+0.84)/\log 0.81]^2 = 179$. Then, under a fixed design the total event size was $D_1^* = 179 * 4 = 716$, 13% higher than the size under the CSH approach. Under the GS design, with the inflation factor `IF`= 1.072, the final stage information was increased and equal to $\mathscr{I}_5 = 179 * 1.072 = 192$. At stage 3 the information was

Figure S2: GS design: Required event sizes at interim analyses (left panel) and conditional power as a function of the assumed type-1 hazard ratio at stage 3 (right panel), under the CSH and SDH approaches.



$\mathscr{I}_3 = (3/5) * 192 = 115.20$ and thus, the event size was $D_3^* = 115.20 * 4 = 461$ (Figure S2, left panel).

The observed z values were 2.43 and 2.14 at interim stage 3 and final stage 5, respectively. Now, suppose that we are interested in computing the conditional power at stage 3 for a patient who enters the study in a later period with a CSH ratio of 0.80, and thus with a SDH ratio of 0.81. Note that the type-1 CSH ratio quantifies the treatment effect on the type-1 hazard function, whereas the type-1 SDH ratio represents the treatment effect on the log-log scale of type-1 CIF as if the type-2 competing events had not been observed. At stage 3, we also computed the standard errors for the CSH and SDH ratios. For the former, the result was $se(\hat{\beta}_k) = \hat{\beta}_k/z = \log 0.8/(-2) = 0.112$, and for the latter, was $se(\hat{\beta}_k) = \log 0.81/(-2) = 0.105$. Then, the assumed treatment effect at interim stage 3 for the two approaches is: $\beta_{\text{CSH}} = \log 0.80/\sqrt{var(\hat{\beta}_k) * \mathscr{I}_3} = -0.22/(0.112 * \sqrt{101.63}) = -0.194$ and $\beta_{\text{SDH}} = \log 0.81/\sqrt{var(\hat{\beta}_k) * \mathscr{I}_3} = -0.21/(0.105 * \sqrt{115.2}) = -0.186$. Then the CP_3 at stage 3 can be directly computed using the formula for $P_k(\beta)$ given in Section 4.3: $P_3(\beta_{\text{CSH}}) = \Phi[(2 * \sqrt{101.63} - 2.14 * \sqrt{169} + 0.194 * (169 - 101.63))/\sqrt{(169 - 101.63)}] = 0.74$ and $P_3(\beta_{\text{SDH}}) = \Phi[(2 * \sqrt{115.2} - 2.14 * \sqrt{192} + 0.186 *$

$(192 - 115.2))/\sqrt{(192 - 115.2)}] = 0.76$. This indicates that the probability of rejecting the null hypothesis when H_1 is true, if the experiment stops at stage 3, decreases from 0.80 to 0.74 when using the CSH approach, as compared with trial completion in the standard fixed design. The first 407 patients of the planned 678 patients achieved a conditional power of 74% , resulting in the detection of a hazard ratio of 0.80 at a 5% significance level. When the assumed $\log \theta$ is changed, given the other parameters fixed, then the CP_3 changes accordingly, e.g., if we assume $\theta = 0.9$, the CP_3 reduces to 0.45. When using the SDH approach, for a SDH ratio equal to 0.81, the conditional power at stage 3 was 76%, slightly higher than the CP_3 under the CSH approach. However, for such a small amount of change in the hazard ratio (0.01), the stage-3 event size has changed considerably (from 407 to 461) and 54 additional events are required, as compared to the results under the CSH approach (Figure S2, left panel). Additionally, for larger changes in the hazard ratio, e.g., from 0.79 to 0.85, the CP_3 reduces from about 0.80 to 0.60. For instance, if a patient enters the study at an accrual period with assumed treatment effect, $\theta_1 = 0.85$, then the conditional power reduces to 0.60 (Figure $S2$, right panel). Thus, the SDH approach yields a higher D_1^* and a slight gain in power as compared to the CSH approach (depending on the discrepancy between the two hazard ratios).

An easy way to decide on trial continuation or stoppage at a certain stage is to calculate the futility index, given as $F_k = 1-$ CP. For example, with a hazard ratio of 0.8, at stage 3 this index is $\tilde{F}_3 = 1 - 0.74 = 0.26$ for the CSH approach and $F_3^* = 1 - 0.76 = 0.24$ for the SDH approach. If the index is found greater than 0.8, which means that the conditional power is lower than 0.20, then the clinical trial may be stopped because there is a very small chance of achieving statistical significance of the treatment effect.