EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 June 2018
EMA/CHMP/SAWP/381415/2018
Procedure No.: EMEA/H/SAB/090/1/2018
Product Development Scientific Support Department

Treatment effect measures when using recurrent event endpoints – Qualification Opinion List of Issues regarding provided simulation exercises

Summary

A request for a qualification opinion entitled “Clinically interpretable treatment effect measures based on recurrent event endpoints that allow for efficient statistical analyses” has been issued by a number of renowned statisticians. The request is centred on two examples (relapsing remitting multiple sclerosis (rrMS) and chronic heart failure (CHF)) representing situations where recurrent event analyses may offer opportunities to describe a clinically relevant treatment effect. Whereas in the first example recurrent event analyses for relapses have been used for decision making during drug licensing, experiences are still limited with the use of recurrent re-hospitalisations for worsening heart failure in the latter indication that is distinct in that death is still frequent in heart failure studies.

From a statistical perspective the intercurrent event “death” obviously censors further observation of the recurrent event endpoint under investigation, but additional consideration should be given to the fact that further re-hospitalisations are impossible and the time-point of censoring is not just a lower boundary for the time to the next rehospitalisation to be observed.

In consequence, both, statistical challenges regarding methodological aspects and medical interpretation of outcome will have to be addressed in the end.

Scientific discussion

A wealth of information has been provided and a large number of simulations have been done and discussed. Groundwork regarding recurrent event analysis has been prepared in an extensive report that is under review regarding the aforementioned challenges.

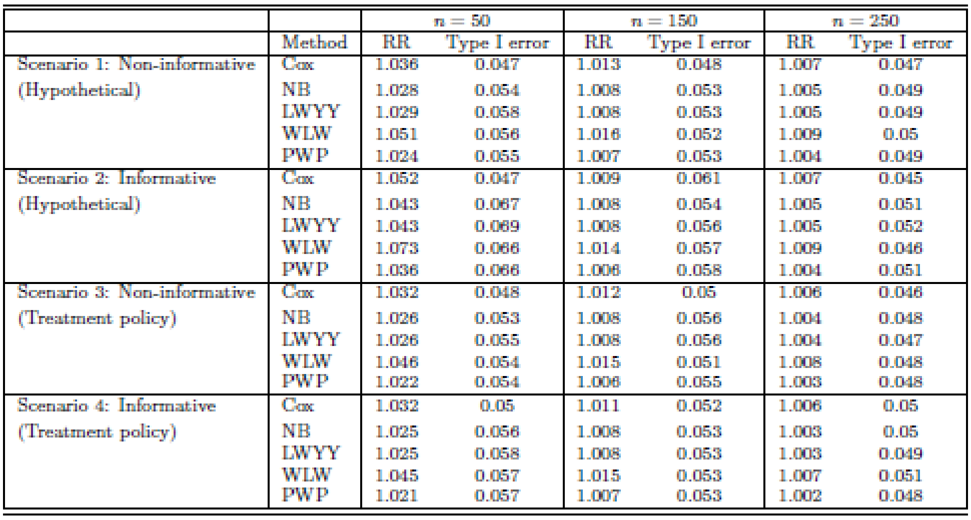
In an initial phase of assessment some open issues have been identified that require clarification and possibly an amendment and even extension of the currently provided simulation exercises.

Regarding scenarios without a terminal event, some questions arise relating to the simulations presented in table 7. Firstly, it is not clear why every estimate of the RR in the table should be over 1.0. A random scattering of values above and below 1.0 would have been expected. One possible reason would be if the averaging across simulation runs had been done on the arithmetic rather than logarithmic scale. If this is not the reason, an explanation for and discussion of the systematic finding would be helpful.

Regarding the apparent loss of type I error control with smaller sample sizes, interpretation of the table would be easier if the simulations were done using 1-sided tests at the 2.5% level, rather than 2-sided 5% tests.

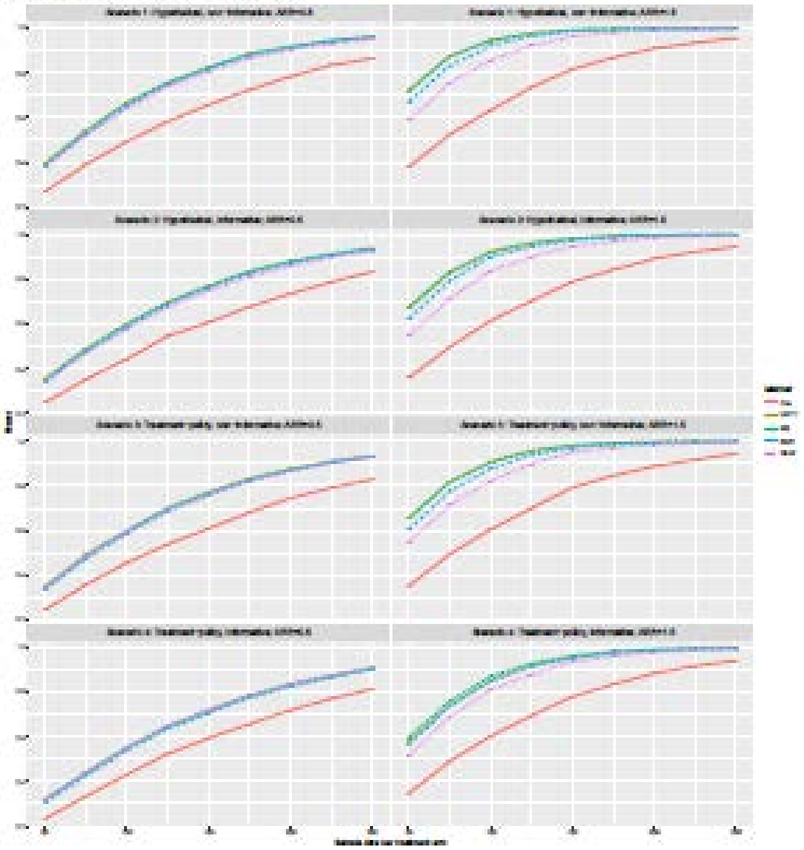
It would also be valuable to include the log-rank test in the table (although no estimate of the RR would be available) as this is often the method used for the initial significance test in time-to-first-event analyses. This would also be valuable in the simulations of power, such as were presented in Figure 7.

Table 7: Settings without terminal event: Mean treatment effect estimates and type I error rate under four scenarios based on 10'000 clinical trial simulations, $RR = 1$, $\theta = 0.25$, $\lambda_0 = 0.5$.



		$n = 50$		$n = 150$		$n = 250$	
	Method	RR	Type I error	RR	Type I error	RR	Type I error
Scenario 1: Non-informative (Hypothetical)	Cox	1.036	0.047	1.013	0.048	1.007	0.047
	NB	1.028	0.054	1.008	0.053	1.005	0.049
	LWYY	1.029	0.058	1.008	0.053	1.005	0.049
	WLW	1.051	0.056	1.016	0.052	1.009	0.05
	PWP	1.024	0.055	1.007	0.053	1.004	0.049
Scenario 2: Informative (Hypothetical)	Cox	1.052	0.047	1.009	0.061	1.007	0.045
	NB	1.043	0.067	1.008	0.054	1.005	0.051
	LWYY	1.043	0.069	1.008	0.056	1.005	0.052
	WLW	1.073	0.066	1.014	0.057	1.009	0.046
	PWP	1.036	0.066	1.006	0.058	1.004	0.051
Scenario 3: Non-informative (Treatment policy)	Cox	1.032	0.048	1.012	0.05	1.006	0.046
	NB	1.026	0.053	1.008	0.056	1.004	0.048
	LWYY	1.026	0.055	1.008	0.056	1.004	0.047
	WLW	1.046	0.054	1.015	0.051	1.008	0.048
	PWP	1.022	0.054	1.006	0.055	1.003	0.048
Scenario 4: Informative (Treatment policy)	Cox	1.032	0.05	1.011	0.052	1.006	0.05
	NB	1.025	0.056	1.008	0.053	1.003	0.05
	LWYY	1.025	0.058	1.008	0.053	1.003	0.049
	WLW	1.045	0.057	1.015	0.053	1.007	0.051
	PWP	1.021	0.057	1.007	0.053	1.002	0.048

Figure 7: Setting without terminal event: Statistical power at varied sample size under four scenarios based on 10'000 clinical trial simulations, $RR = 0.65$, $\theta = 0.25$, $\lambda_0 = 0.5, 1.5$.



For the settings with a terminal event similar issues arise regarding type I error, as shown in table 11, with all estimates above 1.0 (even in the global null situation) and the difficulty of interpreting 2-side 5% tests as compared to 1-sided 2.5% tests. To match with table 7 presentation of results with varying sample size would be useful. Also a row could be provided for HRCV = 1.25 to match other tables. HRCV could also be varied for Estimand 2, despite this meaning that the figures would no longer strictly represent type I error for that estimand.

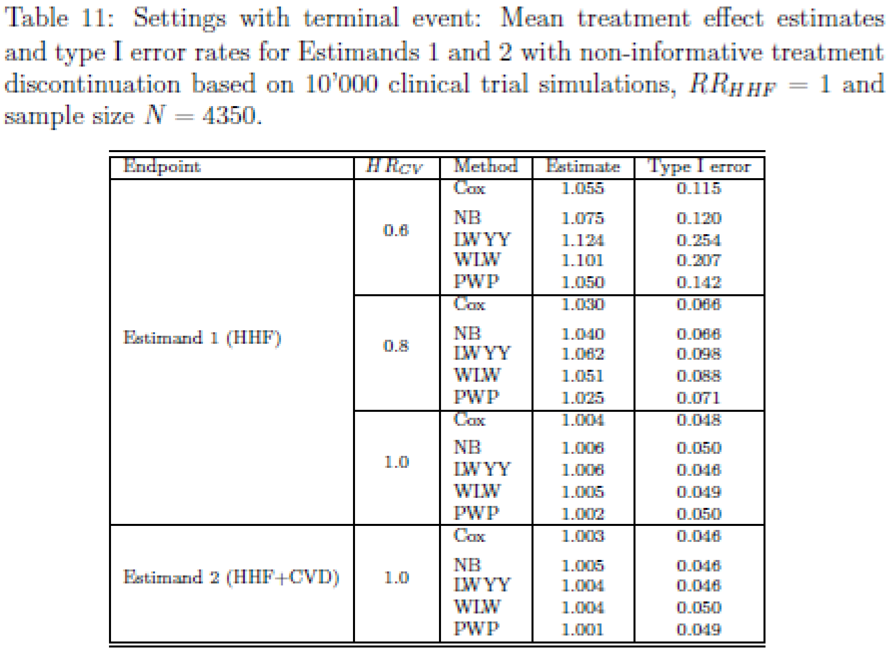


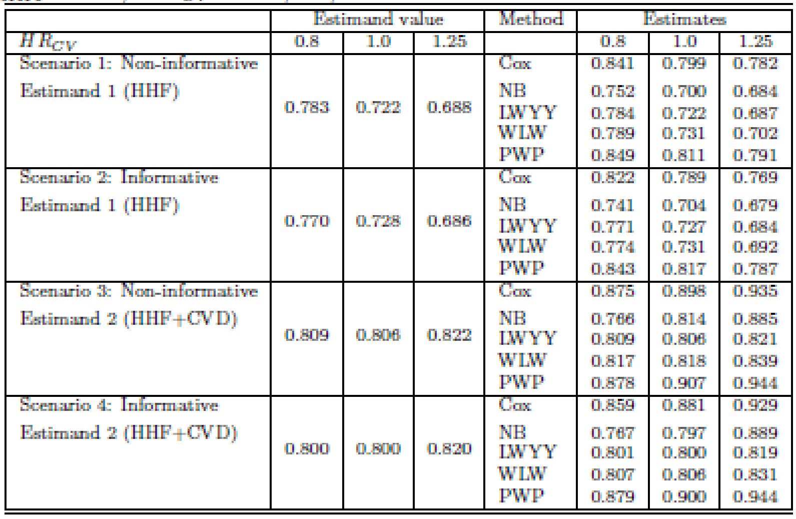
Table 11: Settings with terminal event: Mean treatment effect estimates and type I error rates for Estimands 1 and 2 with non-informative treatment discontinuation based on 10'000 clinical trial simulations, $RR_{HHF} = 1$ and sample size $N = 4350$.

Endpoint	HR_{CV}	Method	Estimate	Type I error
Estimand 1 (HHF)	0.6	Cox	1.055	0.115
		NB	1.075	0.120
		LWYY	1.124	0.254
		WLW	1.101	0.207
		PWP	1.050	0.142
	0.8	Cox	1.030	0.066
		NB	1.040	0.066
		LWYY	1.062	0.098
		WLW	1.051	0.088
		PWP	1.025	0.071
	1.0	Cox	1.004	0.048
		NB	1.006	0.050
		LWYY	1.006	0.046
		WLW	1.005	0.049
		PWP	1.002	0.050
Estimand 2 (HHF+CVD)	1.0	Cox	1.003	0.046
		NB	1.005	0.046
		LWYY	1.004	0.046
		WLW	1.004	0.050
		PWP	1.001	0.049

In the scenario with a terminal event two estimands were considered. Firstly, the ratio of the number of recurrent events (in this case hospitalisations), and secondly the ratio of events, where the terminal even (death) was also counted as an event.

Both these estimands seem to exhibit concerning properties. Neither truly estimate the effect on the recurrent event independent of the terminal event, or present a coherent combination of the two for an overall evaluation of the two factors together (adding one additional recurrent event to represent a terminal even seems arbitrary).

Table 8: Settings with terminal event (Estimand vs Estimate): True estimand values under four scenarios, as well as the treatment effects estimates from five approaches. Simulated data for 100'000 patients are generated with $RR_{HHF} = 0.7$, $HR_{CV} = 0.8; 1.0; 1.25$.



	Estimand value			Method	Estimates		
HR_{CV}	0.8	1.0	1.25		0.8	1.0	1.25
Scenario 1: Non-informative Estimand 1 (HHF)	0.783	0.722	0.688	Cox	0.841	0.799	0.782
				NB	0.752	0.700	0.684
				LWYY	0.784	0.722	0.687
				WLW	0.789	0.731	0.702
				PWP	0.849	0.811	0.791
Scenario 2: Informative Estimand 1 (HHF)	0.770	0.728	0.686	Cox	0.822	0.789	0.769
				NB	0.741	0.704	0.679
				LWYY	0.771	0.727	0.684
				WLW	0.774	0.731	0.692
				PWP	0.843	0.817	0.787
Scenario 3: Non-informative Estimand 2 (HHF+CVD)	0.809	0.806	0.822	Cox	0.875	0.898	0.935
				NB	0.766	0.814	0.885
				LWYY	0.809	0.806	0.821
				WLW	0.817	0.818	0.839
				PWP	0.878	0.907	0.944
Scenario 4: Informative Estimand 2 (HHF+CVD)	0.800	0.800	0.820	Cox	0.859	0.881	0.929
				NB	0.767	0.797	0.889
				LWYY	0.801	0.800	0.819
				WLW	0.807	0.806	0.831
				PWP	0.879	0.900	0.944

In table 8 the risk ratio for hospitalization is 0.7, but depending on the rates of terminal events the estimand value alters, and with estimand 1 gets more impressive if the treatment has an adverse effect on the terminal events. Similarly, treatments which are reducing the rate of terminal events are penalised. This does not occur with estimand 2 in these examples, but that is partly a function of follow-up time and the rates of each type of event, and it seems likely that it would happen for other durations of study or different choices of event rate parameters. If the intention here is to use the estimation methods to estimate the effect on hospitalisations independent of the effect on the terminal event, then an estimand that gives 0.7 regardless of the terminal even effect would seem to be desirable. If this is not the intention and a combination of terminal and recurrent events is the intention, then a more sophisticated joint modelling approach than just adding in the terminal event as an additional event seems required. Thoughts turn to rank-based approaches where patients are ordered based on their outcome on both variables.

While the methods, particularly LWYY seem to estimate the estimands well, the estimands themselves are currently questioned. Rank based methods such as the win-ratio, while maybe lacking power, at least do not have that property of these estimands, though they do lead to weighting issues regarding the importance of the terminal event.

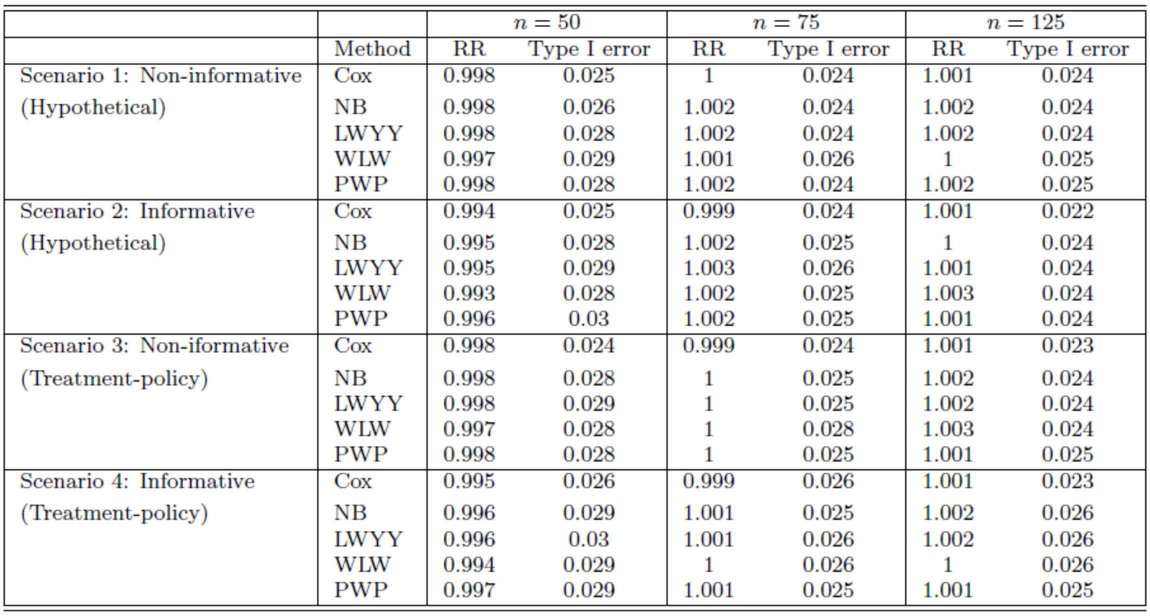
Based on the discussion above the Scientific Advice Working Party (SAWP) determined that the Applicant should discuss a list of issues, before advice can be provided. On the 21st of March 2018 the list of issues were sent to the applicant. On the 6th of April 2018 the applicant provided written responses to the list. The first list of issues and the preliminary qualification team feedback on the written responses are provided below.

For the simulations of scenarios with no terminal event

Question 1.1
For the simulations of type I error, please provide the tables using 1-sided tests at the 2.5% level rather than 2-sided tests at the 5% level. Please also include the log-rank test as part of the simulations. Please then re-discuss the issue of type I error control in studies with smaller sample sizes.

Novartis Reply: We agree that simulations using 1-sided tests at the 2.5% level may provide additional information. We present Table 7 using 1-sided tests at the 2.5% level while focusing on smaller sample sizes (n = 50, 75 and 125 per group); see Table 7A below. Table 7A shows that the 1-sided type I error inflation for smaller sample sizes (n=50) is not as pronounced as for 2-sided tests, and that the 1-sided type I error is well controlled at n $\geq$ 75 per arm. We expect the results to be similar in spirit for other scenarios. Would you thus agree that Table 7A is providing sufficient insights to the similarities of the findings based on 1-sided and 2-sided tests?

Table 7A: Mean treatment effects estimates (geometric mean) and Type I error rates (1-sided tests, nominal significance level $\alpha = 0.025$) under four scenarios, with treatment effect size $\mathrm{RR} = 1$, baseline recurrent event rate $\lambda_0 = 0.5$, and dispersion parameter $\theta = 0.25$.



		$n = 50$		$n = 75$		$n = 125$	
	Method	RR	Type I error	RR	Type I error	RR	Type I error
Scenario 1: Non-informative	Cox	0.998	0.025	1	0.024	1.001	0.024
(Hypothetical)	NB	0.998	0.026	1.002	0.024	1.002	0.024
	LWYY	0.998	0.028	1.002	0.024	1.002	0.024
	WLW	0.997	0.029	1.001	0.026	1	0.025
	PWP	0.998	0.028	1.002	0.024	1.002	0.025
Scenario 2: Informative	Cox	0.994	0.025	0.999	0.024	1.001	0.022
(Hypothetical)	NB	0.995	0.028	1.002	0.025	1	0.024
	LWYY	0.995	0.029	1.003	0.026	1.001	0.024
	WLW	0.993	0.028	1.002	0.025	1.003	0.024
	PWP	0.996	0.03	1.002	0.025	1.001	0.024
Scenario 3: Non-iformative	Cox	0.998	0.024	0.999	0.024	1.001	0.023
(Treatment-policy)	NB	0.998	0.028	1	0.025	1.002	0.024
	LWYY	0.998	0.029	1	0.025	1.002	0.024
	WLW	0.997	0.028	1	0.028	1.003	0.024
	PWP	0.998	0.028	1	0.025	1.001	0.025
Scenario 4: Informative	Cox	0.995	0.026	0.999	0.026	1.001	0.023
(Treatment-policy)	NB	0.996	0.029	1.001	0.025	1.002	0.026
	LWYY	0.996	0.03	1.001	0.026	1.002	0.026
	WLW	0.994	0.029	1	0.026	1	0.026
	PWP	0.997	0.029	1.001	0.025	1.001	0.025

We also agree that the log-rank test is often the method used for the initial significance test in time-to-first-event analyses. The log-rank test is identical to the score test of the Cox regression and very similar to the Wald test used in Table 7 (as no covariates are included); see for example Andersen et al (1993), page 487. Thus we believe that the results shown in Table 7 (and elsewhere in the original request document) are representative for the findings to be expected based on the log-rank test.

Qualification team comments:
No further information is required for SAWP to be able to provide an opinion. There is agreement that Cox-Regression for the purpose of these qualitative investigations is sufficient and that no additional simulation outcome needs to be provided for the log-rank test. As a general comment, wherever feasible, results from one-sided testing should be provided as decision making is clearly directional and the fact that the impact of treatment on the assessment of two endpoints is needed clearly complicates assessment.

Question 1.2
Please discuss why in settings with no terminal event where the true RR=1.0 the estimate from all methods tends to favor the control group.

Novartis Reply: As pointed out by the reviewers, the reason for all estimates being larger than one is that in the original request document the averaging across simulation runs was done on the arithmetic rather than on logarithmic scale. Table 7A (see Question 1.1) shows simulation results when averaging across simulation runs is done on the logarithmic scale. The difference between arithmetic mean and geometric mean is small, and the geometric mean estimates are scattered above and below 1 as expected.

Qualification team comments:
The applicant’s response is plausible, however, for the smallest investigated sample-size all estimates are still less than one. Please comment whether lacking asymptotic normality can be excluded as a

reason and bias is truly absent (e.g. by providing results for an even larger sample-size n). The question should be further addressed in writing and during the discussion meeting.

Question 1.3
For the simulations of power please also include the log-rank test as this is approach more likely to be used for a significance test than Cox regression.
Novartis Reply: We believe that this question has already been addressed, therefore we kindly refer to our response to Question 1.1.

Qualification team comments:
No further information is required for SAWP to be able to provide an opinion. See also comments in question 1.1.

For the situation where there is a terminal event:
Question 2.1:

Please present Table 11 using 1-sided tests at the 2.5% level instead of 2-sided 5% tests. Please also add a row for HR_{CV}=1.25, add the log-rank test to the table, vary HR_{CV} for estimand 2 and provide results for varying sample size.

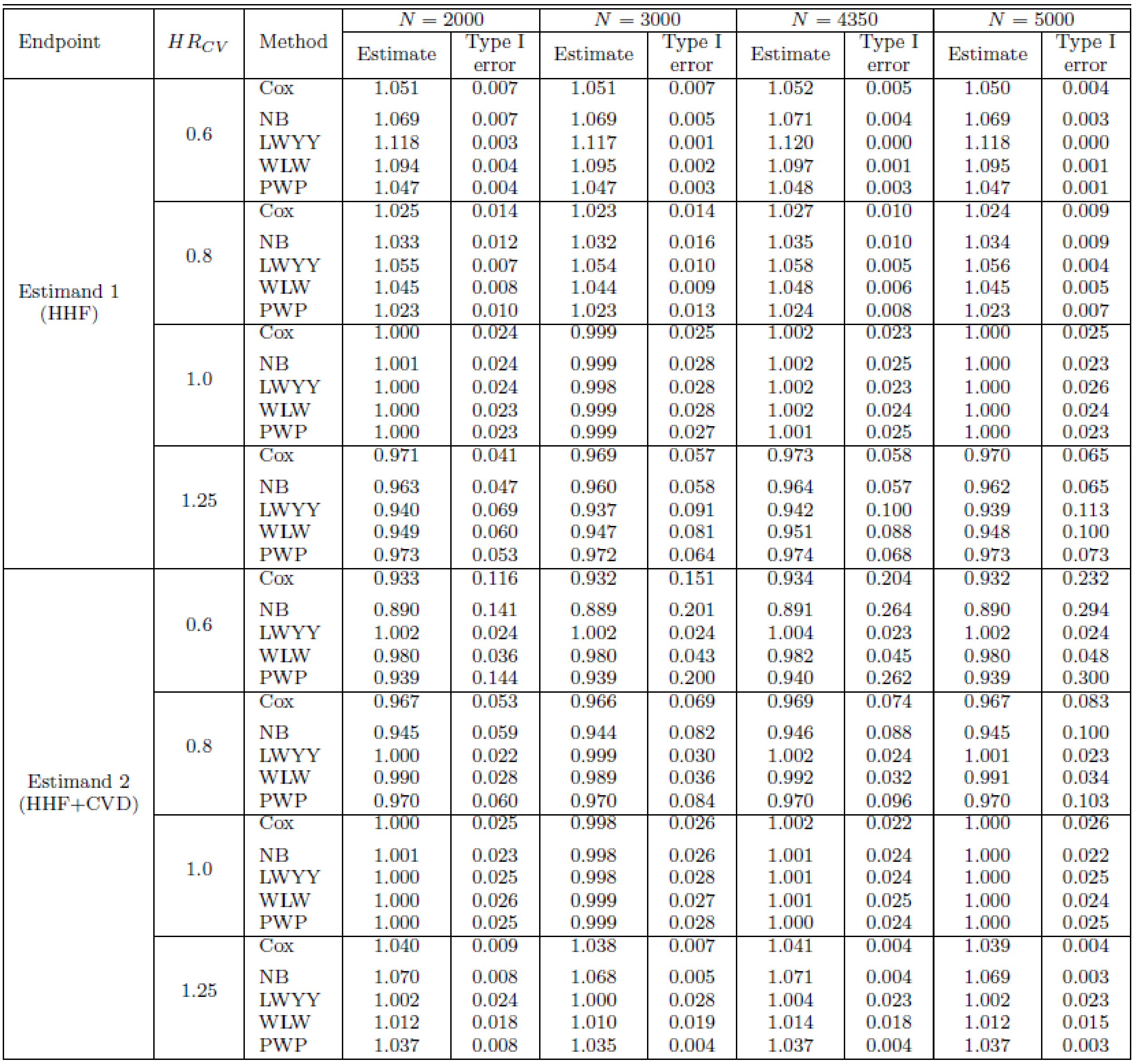
Novartis Reply: We present Table 11 using 1-sided tests at the 2.5% level, see Table 11A below. We also included varying sample sizes and added HR_{CV}=1.25 for Estimand 1 and HR_{CV}=0.6, 0.8, 1.25 for Estimand 2. Furthermore, the averaging across simulation runs is now done on the logarithmic scale instead of averaging on the arithmetic scale. As for the response to Question 1.1 for the non-terminal event scenario, we did, however, not include the results based on the log-rank test.

For both estimands the type I error remains under control under the global null hypothesis (RR_{HHF}=1 and HR_{CV}=1) for all considered sample sizes.

With the use of 1-sided tests and including HR_{CV}=1.25 for Estimand 1, we observe a type 1 error inflation in favor of the treatment that has a negative effect on CV death. The reason is that for HR_{CV}=1.25 especially the severely ill patients in the treatment group (i.e. those with high frailty) die earlier and therefore contribute fewer hospitalizations. This makes the treatment appear more effective in reducing HHF. This is in line with our previous observations for Estimand 1 with RR_{HHF}=1 and HR_{CV}< 1 (see second bullet point on page 64 of the original request document). Additionally, for HR_{CV}=1.25 the type I error increases with increasing sample size, because the estimated treatment effect is below 1 (see reply to Question 2.4) and a larger sample size will lead to a smaller variance of the test statistics and ultimately to more frequent rejections.

In contrast, for Estimand 2 we observe in Table 11A that the probability to reject in favor of the treatment with positive effect on CV death is larger than α. However, we would not refer to this as a Type I error when HR_{CV}≠1. Note that the original Table 11 only included results for $HR_{CV} =$ 1 because RR_{HHF}=1 and HR_{CV}=1 jointly constitute the global null hypothesis for Estimand 2. When including HR_{CV}≠1, a reference to "Power" seems more appropriate. As expected, the power then increases with increasing sample size. An exception is the LWYY method, see Appendix A.2.3.1 in the original request document, where similar to other simulation settings presented in the original request document the power is largely unaffected by HR_{CV}.

Table 11A: Mean treatment effects estimates (geometric mean) and Type I error rates (1-sided tests, nominal significance level $\alpha = 0.025$) for Estimand 1 (HHF) and Estimand 2 (HHF + CVD) with non-informative treatment discontinuation and $RR_{HHF} = 1$.



Endpoint	HR_{CV}	Method	$N = 2000$		$N = 3000$		$N = 4350$		$N = 5000$	
			Estimate	Type I error	Estimate	Type I error	Estimate	Type I error	Estimate	Type I error
Estimand 1 (HHF)	0.6	Cox	1.051	0.007	1.051	0.007	1.052	0.005	1.050	0.004
		NB	1.069	0.007	1.069	0.005	1.071	0.004	1.069	0.003
		LWYY	1.118	0.003	1.117	0.001	1.120	0.000	1.118	0.000
		WLW	1.094	0.004	1.095	0.002	1.097	0.001	1.095	0.001
		PWP	1.047	0.004	1.047	0.003	1.048	0.003	1.047	0.001
	0.8	Cox	1.025	0.014	1.023	0.014	1.027	0.010	1.024	0.009
		NB	1.033	0.012	1.032	0.016	1.035	0.010	1.034	0.009
		LWYY	1.055	0.007	1.054	0.010	1.058	0.005	1.056	0.004
		WLW	1.045	0.008	1.044	0.009	1.048	0.006	1.045	0.005
		PWP	1.023	0.010	1.023	0.013	1.024	0.008	1.023	0.007
	1.0	Cox	1.000	0.024	0.999	0.025	1.002	0.023	1.000	0.025
		NB	1.001	0.024	0.999	0.028	1.002	0.025	1.000	0.023
		LWYY	1.000	0.024	0.998	0.028	1.002	0.023	1.000	0.026
		WLW	1.000	0.023	0.999	0.028	1.002	0.024	1.000	0.024
		PWP	1.000	0.023	0.999	0.027	1.001	0.025	1.000	0.023
	1.25	Cox	0.971	0.041	0.969	0.057	0.973	0.058	0.970	0.065
		NB	0.963	0.047	0.960	0.058	0.964	0.057	0.962	0.065
		LWYY	0.940	0.069	0.937	0.091	0.942	0.100	0.939	0.113
		WLW	0.949	0.060	0.947	0.081	0.951	0.088	0.948	0.100
		PWP	0.973	0.053	0.972	0.064	0.974	0.068	0.973	0.073
Estimand 2 (HHF+CVD)	0.6	Cox	0.933	0.116	0.932	0.151	0.934	0.204	0.932	0.232
		NB	0.890	0.141	0.889	0.201	0.891	0.264	0.890	0.294
		LWYY	1.002	0.024	1.002	0.024	1.004	0.023	1.002	0.024
		WLW	0.980	0.036	0.980	0.043	0.982	0.045	0.980	0.048
		PWP	0.939	0.144	0.939	0.200	0.940	0.262	0.939	0.300
	0.8	Cox	0.967	0.053	0.966	0.069	0.969	0.074	0.967	0.083
		NB	0.945	0.059	0.944	0.082	0.946	0.088	0.945	0.100
		LWYY	1.000	0.022	0.999	0.030	1.002	0.024	1.001	0.023
		WLW	0.990	0.028	0.989	0.036	0.992	0.032	0.991	0.034
		PWP	0.970	0.060	0.970	0.084	0.970	0.096	0.970	0.103
	1.0	Cox	1.000	0.025	0.998	0.026	1.002	0.022	1.000	0.026
		NB	1.001	0.023	0.998	0.026	1.001	0.024	1.000	0.022
		LWYY	1.000	0.025	0.998	0.028	1.001	0.024	1.000	0.025
		WLW	1.000	0.026	0.999	0.027	1.001	0.025	1.000	0.024
		PWP	1.000	0.025	0.999	0.028	1.000	0.024	1.000	0.025
	1.25	Cox	1.040	0.009	1.038	0.007	1.041	0.004	1.039	0.004
		NB	1.070	0.008	1.068	0.005	1.071	0.004	1.069	0.003
		LWYY	1.002	0.024	1.000	0.028	1.004	0.023	1.002	0.023
		WLW	1.012	0.018	1.010	0.019	1.014	0.018	1.012	0.015
		PWP	1.037	0.008	1.035	0.004	1.037	0.004	1.037	0.003

Qualification team comments: No further information is required for SAWP at this stage of the procedure. Simulations including the log-rank-test are not necessarily needed and Cox-regression models should suffice to reflect the outcome of time to first event analyses that should be unbiased against negative correlation between treatment effects on mortality and on rehospitalisation for worsening hear-failure. Most challenging is the situation where a terminal event occurs in a non-negligible proportion of cases. While it is formally correct (as pointed out in response to question 2.1), that HRCV<>1 is not part of the global null-hypothesis, the question can be easily rephrased regarding the power to detect such deviations from the null-hypothesis (i.e. that there is a detriment of the new treatment on cardiovascular (or overall) mortality). Moreover it has to be noted that also the conclusions on HFH are biased. This obviously needs to be addressed once the implications for decision making are discussed from a medical perspective.

Question 2.2:
Please provide additional simulations with higher mortality (~ 20%, 40% overall in the trial) to better understand the degree of type-1-error increases and behaviour of estimands 1 and 2 with varying HR_{CV} in these situations.

Novartis Reply: In an overview of published heart failure trials by Anker and McMurray (2012) the proportion of CV death events of all composite events (CV death + HHFs) was shown to be relatively stable at around 30% when considering either a time-to-first-event or a recurrent events endpoint, see the table below extracted from the article. The list of trials included in the review covers a range of overall CV mortality. For example, in the CHARM-Added trial 27.3% patients died for CV causes in the placebo arm during 41 month of median follow-up, while in the CHARM-preserved trial 11.3% patients had a CV death in the placebo arm during 36.6 months of median follow-up. As a comparison, the simulation performed in the original request document has for the base case and non-informative treatment discontinuation an overall CV mortality of 12.5% in the placebo arm during 38.5 months of median follow-up, so in this respect is similar to the CHARM-Preserved study.

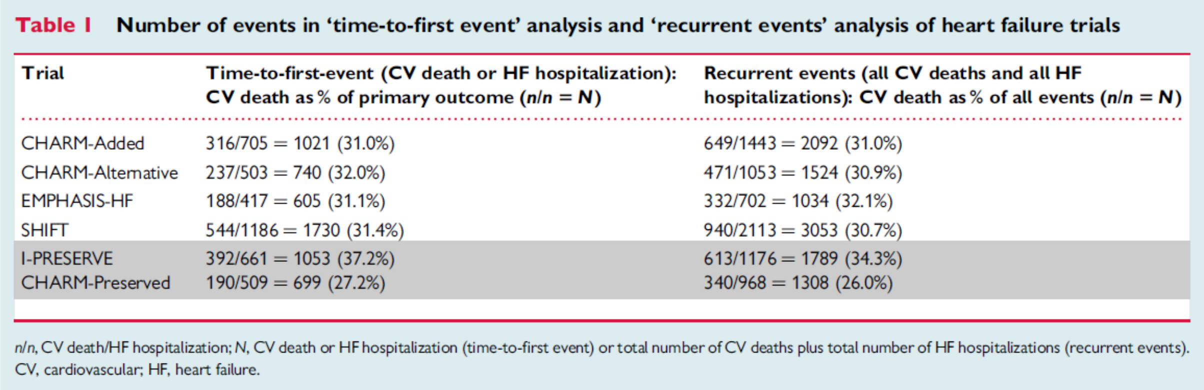


Table 1 Number of events in 'time-to-first event' analysis and 'recurrent events' analysis of heart failure trials

Trial	Time-to-first-event (CV death or HF hospitalization): CV death as % of primary outcome (*n*/*n* = *N*)	Recurrent events (all CV deaths and all HF hospitalizations): CV death as % of all events (*n*/*n* = *N*)
CHARM-Added	316/705 = 1021 (31.0%)	649/1443 = 2092 (31.0%)
CHARM-Alternative	237/503 = 740 (32.0%)	471/1053 = 1524 (30.9%)
EMPHASIS-HF	188/417 = 605 (31.1%)	332/702 = 1034 (32.1%)
SHIFT	544/1186 = 1730 (31.4%)	940/2113 = 3053 (30.7%)
I-PRESERVE	392/661 = 1053 (37.2%)	613/1176 = 1789 (34.3%)
CHARM-Preserved	190/509 = 699 (27.2%)	340/968 = 1308 (26.0%)

n/*n*, CV death/HF hospitalization; *N*, CV death or HF hospitalization (time-to-first event) or total number of CV deaths plus total number of HF hospitalizations (recurrent events). CV, cardiovascular; HF, heart failure.

If the objective of additional simulations with increasing CV mortality rates is to be representative of a heart failure population, we propose to increase the HHF rate such that the proportion of CV death of all events is kept roughly at 30%. Increasing the mortality rate without changing the rate of HHF could potentially increase the generalizability of the results to other chronic indications with high terminal event rate but would no longer be representative of heart failure trials. In addition, if the rate for mortality events is as large as the rate of recurrent events or even larger, the clinical community may favor the investigation of time-to-first composite or time-to-mortality endpoints.

For the requested additional simulations to better understand the type-1-error behaviour with higher mortality, should the rate of heart failure hospitalizations be increased at the same time as increasing the mortality rate? If so, do you agree with our proposal above, i.e. to also increase the HHF rate such that the proportion of CV death of all events is kept roughly at 30%?

Preliminary qualification team comments: It is agreed that the rate of heart failure hospitalizations should be increased at the same time as increasing the mortality rate. Different proportions of CV death should be investigated to further elucidate the impact of the negatively correlated effects on re-hospitalisation and mortality and particularly to understand the impact on the estimands as proposed, or requested. It is supported that different expectations regarding the terminal event may lead to different preferences regarding the choice of the analysis, but until now the discussion on the utility of recurrent hospitalisations for worsening heart failure was not perceived as specific for the situation of heart failure with preserved ejection fraction or other selection of the patient population that are of low risk for the terminal event. The question should be further addressed in writing and during the discussion meeting.

Question 2.3:
Please discuss how it is envisaged that estimands 1 and 2 would be used in practice. Are they intended to be interpreted as an estimate of the effect on hospitalisations, or as an overall estimate of the effect of treatment combining both hospitalisations and mortality?

Novartis Reply: Both estimands reflect a patient's forward-looking view of the event rate. A patient may ask: “How many events can I expect to have in the next three years, relative to how long I can expect to live in the next three years?” The proposed estimands adjust for the effect of early termination (death) by accounting for the time at risk.

Estimand 1 (HHF) could be used in settings, where it is expected that test and control treatment will not differ with respect to their effect on terminal events (deaths), based on a strong scientific rationale. In such settings, Estimand 1 would measure the treatment effect on hospitalizations while alive, similar to settings without terminal events. The effect of treatments on death should be evaluated as well, and would have to be taken into account when interpreting Estimand 1.

Estimand 2 (HHF+CVD) provides an overall treatment effect, including both hospitalizations and mortality, i.e. counts all disease-related “bad events” (hospitalizations for heart failure or cardiovascular deaths) while alive. It should be noted that as in other settings where composite estimands are used, the individual components would still be evaluated, in particular the treatment effect on death, and taken into account when interpreting the results. Estimand 2 weights all bad events equally, and can be seen as a natural extension of time-to-first-composite-event analyses (composite of first HHF or CVD) to the recurrent HHF setting. Other weightings are discussed in response to Question 2.5 and Section 3.2.1.6.2 of the original request document.

Estimand 1 and Estimand 2 appear to be understandable and meaningful for patients and clinicians, have a causal interpretation, and are estimable with minimal assumptions.

We would like to illustrate this further for Estimand 2, however, the following considerations also apply for Estimand 1.

Using a standard causal inference framework (e.g. Hernan and Robins, 2018), we consider for each specific patient the bivariate potential outcome (number (#) of bad events, time of death/censoring) if he/she would be randomized to test treatment and control, respectively. Of note, in the actual clinical trial, the outcomes for only one of the treatments will be known, the other being missing. The table below illustrates this potential outcome framework for a trial where each patient is followed for 3.0 years (censoring) or until death. For example, patient Ann would have no bad events and would be alive at 3 years when randomized to Test; however, Ann would have 2 bad events (including death) with a death time of 1.5 years if randomized to Control.

	Test		Control	
Patient	# bad events	Time of death/censoring	# bad events	Time of death/censoring
Ann	0	3.0	2	1.5
Bill	1	3.0	1	2.5
...	...	...	...	...
AVERAGE	0.5	3.0	1.5	2.0

In the example table, the “bad event” rate while alive is 0.17=0.5/3.0 for Test and 0.75=1.5/2.0 for Control. The Estimand 2 is the “bad event” rate ratio, i.e. 0.23=0.17/0.75.

Estimand 2 can simply be defined based on averages (expectations) of potential outcomes, and hence has a causal interpretation. It does not require any model assumptions for the definition. For estimation in randomized clinical trials, both semi-parametric methods (e.g. LWYY, see Appendix A.2.3.1 in original request document) or parametric methods (e.g. NB, see Appendix A.2.2.4 in original request document) can be considered.

As previously mentioned, the above considerations also apply for Estimand 1 (HHF only).

Preliminary qualification team comments:

The applicant agrees that for estimate 1 an additional assessment of treatment effects regarding mortality is needed. Even if for estimand 2 some sort of composite endpoint thinking may be applicable, in both instances the question remains open, how a strategy for decision making should be constructed that optimizes positive conclusions regarding a treatment effect at least excluding a detrimental effect on mortality. From a drug-licensing perspective this is likely the most important question to be addressed. Whereas in end-stage disease (NYHA stage III-V and IV) some but certainly not all patients may be willing to accept a symptomatic improvement even if the treatment is associated with some uncertainty regarding the risk of dying, in earlier stages of the disease, i.e. NYHA II and III, mortality is the key aspect to be investigated. A high level of reassurance that mortality is at least not negatively affected in the whole group of these patients and in relevant subgroups is a prerequisite for designing studies using recurrent hospitalisations for worsening of heart failure analyses. Exploring recurrent hospitalisations for worsening heart failure may be of particular value in patient populations where due to the rarity of the disease information on mortality is limited as it may be the case in patients with rare forms of cardiomyopathy or with heart failure due to hereditary syndromes. In addition, recurrent heart failure event analyses may be an option in phase 2 dose finding studies or in case of an extension of an indication to a related population.

An elaborative discussion on the aspects above needs to take place in the discussion meeting.

Question 2.4:

Please discuss whether there exist alternative estimands which allows an independent evaluation of the true effect on the recurrent event independent of the terminal event (i.e. it would give 0.7 in table 8) which could then be used as a joint endpoint with a separate assessment of the RR for terminal events, and if there is one which methods could estimate it?

Novartis Reply: We would respectfully ask for some clarification on the meaning of the ‘true effect’ in the above question. The value of 0.7 in Table 8 is certainly not the rate ratio for HHF in those alive. It is the value used in the computer simulation to generate recurrent events, both those events which in practice are observed and those events which are unobserved, i.e. those events that do not occur because the subject has died. And it is only by recovering these unobserved events and counting them together with the observed ones that one could obtain the underlying event rates and hence their ratio of 0.7. These considerations are further complicated as treatment discontinuation is an additional relevant intercurrent event in the setting of chronic heart failure studies.

In the chronic heart failure setting, evaluating the effect on the recurrent events *independent* of the terminal event based on observed data is to our knowledge not feasible. Or in other words: Disentangling the recurrent event and terminal event processes is not possible unless these processes are truly independent which would take us back to the scenarios without terminal events.

In our simulations, the association between the recurrent events and the terminal event is modelled through a shared frailty and the value 0.7 should be interpreted conditional on this subject-specific frailty and not as a marginal rate ratio. More specifically, as time progresses patient selection is taking place because the severely ill patients (i.e. those with a higher frailty) die early and patients may discontinue their study treatment. The observed recurrent event rate is thus going to change in those patients remaining alive. If the association between the recurrent events and the terminal event is positive, as simulated in Section 5.2 of the original request document, then the recurrent event rate among survivors will drop as time progresses, while if the association is negative then the recurrent event rate will rise.

In Table 15 (page 138) of Appendix E of the original request document, see also below, we show the impact of the selection process on the true numerical value of Estimand 1 which focuses on the heart failure hospitalizations only. It is these values that the estimator should be recovering rather than the 0.7 used in the simulation process.

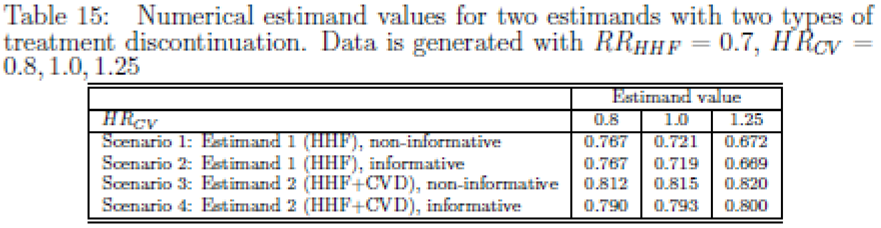


Table 15: Numerical estimand values for two estimands with two types of treatment discontinuation. Data is generated with $RR_{HHF} = 0.7$, $HR_{CV} = 0.8, 1.0, 1.25$

	Estimand value		
HR_{CV}	0.8	1.0	1.25
Scenario 1: Estimand 1 (HHF), non-informative	0.767	0.721	0.672
Scenario 2: Estimand 1 (HHF), informative	0.767	0.719	0.669
Scenario 3: Estimand 2 (HHF+CVD), non-informative	0.812	0.815	0.820
Scenario 4: Estimand 2 (HHF+CVD), informative	0.790	0.793	0.800

In terms of data modelling, one could fit the same joint frailty model that generated the data in our simulation and recover an estimate of the parameter $\exp(\beta)$ (=0.7 in Table 8). This would form an estimator under the assumption that this model is correct. But the underlying estimand is a hypothetical estimand which may not be clinically meaningful as we count both, the events which are observed and those which are unobserved, i.e. those events that do not occur because the subject has died. If the data generating process (the population) did not match the statistical model then the parameter estimate has no clear interpretation.

Preliminary qualification team comments:
This point needs to be kept for the discussion meeting. As outlined in response to question 2.3 both estimands do have a causal interpretation, but (as explained above) it is not fully clear what can be estimated, once the terminal event occurs.

Question 2.5:
Please explore further the power and type I error of rank-based approaches such as win-ratio in various scenarios, and those using weighted composites (of which estimand 2 in your example was a specific case with weight of 1 given to the terminal event).

Novartis Reply: We split our response to your question into two parts. In the first part (see 1. below), we discuss the win ratio as one example of a rank based approach. In the second part (see 2. below), we discuss weighted composites.

1. Win ratio approach
Next to other prioritized outcome measures (e.g. Buyse, 2010), the win ratio has been proposed (Pocock et al., 2012) as an effect measure that considers different outcomes according to their clinical relevance. To the best of our knowledge, the literature about the win ratio focuses on the estimation of the win ratio, distributional properties of these estimators, and on the calculation of confidence intervals for the win ratio. However, win ratio estimands as well as their clinical interpretability and relevance have not been discussed in the literature yet.

Before considering the value of additional simulations, we would like to seek advice from the SAWP on the win ratio approach:

- How would the estimand targeted by the win ratio approach (e.g. according to Pocock et al., 2012) be described using the framework and language suggested by the ICH E9(R1) draft addendum (ICH, 2017)?
- The interpretation of the win ratio critically depends on the follow-up time T (Oakes 2016). To our knowledge this fact has received little to no attention in the medical literature. For illustration, if the follow-up time T converges to infinity in a heart failure trial, every subject will experience a death and the HF hospitalization will have no effect on the win ratio. In other words, the larger the follow-up time T, the less weight we assign to HF hospitalizations. How should the win ratio approach be used in clinical research given that the interpretation of any results will critically depend on the follow-up time, i.e. results can generally not be generalized to other follow-up schemes?
- How should recurrent hospitalizations for heart failure be included into the win ratio approach? For example, the comparison could be based on the time-to-first HHF (Pocock et al., 2012) or the rate of HHFs (Rogers et al. 2016).
- Is the matched or the unmatched version of the win ratio approach more clinically relevant? In case of the matched approach, how should patients be matched?
- In practice, the interpretability and efficiency of the win ratio approach seems to heavily depend on the censoring distribution. The findings of any simulation study will thus also

strongly depend on the assumed censoring distribution, which might attenuate the usefulness of simulation results. Would you agree?

2. Weighted composites

In a weighted composite endpoint, the individual components of the endpoint are assigned weights. The weights are chosen to reflect the clinical importance of the individual components of the composite endpoint. A number of statistical methods considering weighting of endpoints have been considered in recent years, such as the Mao and Lin (2016) or Luo et al. (2017). However, as highlighted by Anker et al. (2016): "[Statistical methods to weight outcomes] are limited by lack of consensus on the relative weighting of events and inconsistency across studies." Thus, while from a statistical perspective weighted outcomes might be appealing, the definition of weights in a manner that is scientifically justified and agreed upon within the clinical community is not feasible from a clinical perspective. A more detailed discussion of these aspects is given in Section 3.2.1.6.2 of the original request document.

As pointed out by the reviewers, Estimand 2 also constitutes a weighted endpoint in the sense that a cardiovascular hospitalization is weighted the same as a cardiovascular death.

Since we have already considered a weighted endpoint (Estimand 2) and the lack of consensus in the clinical community on an appropriate weighted composite endpoint, would you agree that additional simulation focusing on weighted composite endpoints would be of limited value unless the weighted composite is informed by a clinical rational/consensus?

Preliminary qualification team comments:

This point needs to be kept for the discussion meeting.

Question 2.6:

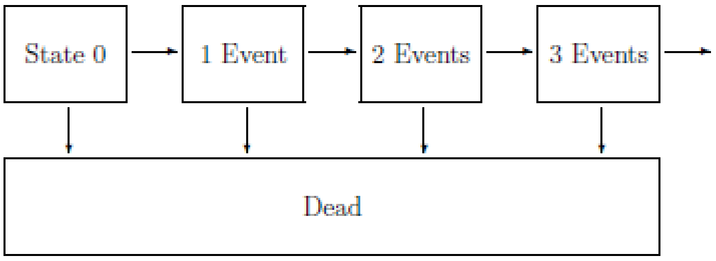
Discuss the utility of multi-stage models to simulate and estimate both, the effect of treatment on mortality and, the effect on HFH. These estimates should be investigated in simulations regarding their statistical properties, interpretability, and yardsticks to their utilization.

Novartis Reply: The utility of multi-state models in the presence of terminal events was discussed in the Appendix of the original request document; see for example A.1.5 and A.2.5.

Moreover, some of the models, which were explored in the simulation study, are in fact specific examples of multi-state models, e.g. the PWP and the Negative Binomial models, see also Appendix A.2.2 of the original request document. The simulation results for the associated models can thus be considered as multi-state model results, i.e. the modeling assumptions and partial likelihoods correspond to particular multi-state models.

Besides these models, one could consider more general multi-state models as depicted in Figure 14 in Appendix A.1.5 of the original request document.

Figure 14: Recurrent events considered as a multi-state model with a terminal event.



This would allow the estimation of various hazard functions as well as their dependence on the number of previous events, the treatment and other covariates. Such general models, however, have several challenges:

- Treatment effects within particular higher-order transitions are difficult to interpret as they represent effects patients will benefit from only if they have entered that particular state before. In particular, these comparisons are no longer protected by randomization.
- Estimating the various transition hazards sounds attractive at first glance; however, it is not obvious how to combine this information into interpretable and clinically meaningful overall treatment effect measures. Therefore, the key challenges mentioned in Section 3.2 of the original request document still remain.
- Estimation of specific transition hazards to and from certain higher event numbers might not be feasible due to the sparseness of data.

Would you agree that we have already provided a discussion on multi-state models – including simulations for specific multi-state models under a broad range of scenarios?

If simulations for additional multi-state models are required, we would like to seek advice from the SAWP on the multi-state models of interest, e.g.

- Which overall treatment effect measure (estimand) should we target?
- How many states should the model have?
- Should the treatment effects for the different transitions all vary?

Preliminary qualification team comments:
A large number of different estimates for transition rates can be estimated from the data, but simplifications may be possible, as well (e.g. why not assume that some of the parameters are constant?). For simplicity, at the moment multi-stage models may be dropped from the discussion to first precisely clarify the appropriate regulatory question.

The Scientific Advice Working Party (SAWP) determined that the Applicant should discuss a list of issues, before advice can be provided.

Pending Issues (from the first round of discussions)
Question 1.2: Please discuss why in settings with no terminal event where the true RR=1.0 the estimate from all methods tends to favor the control group. Please comment whether lacking asymptotic normality can be excluded as a reason and bias is truly absent (e.g. by providing results for an even larger sample-size n).

Question 2.2: Please provide additional simulations with higher mortality (~ 20%, 40% overall in the trial) to better understand the degree of type-1-error increases and behaviour of estimands 1 and 2 with varying HR_{CV} in these situations.

Question 2.3: Please discuss how it is envisaged that estimands 1 and 2 would be used in practice. Are they intended to be interpreted as an estimate of the effect on hospitalisations, or as an overall estimate of the effect of treatment combining both hospitalisations and mortality?

Question 2.4: Please discuss whether there exist alternative estimands which allows an independent evaluation of the true effect on the recurrent event independent of the terminal event (i.e. it would give 0.7 in table 8) which could then be used as a joint endpoint with a separate assessment of the RR for terminal events, and if there is one which methods could estimate it?

Question 2.5: Please explore further the power and type I error of rank-based approaches such as win-ratio in various scenarios, and those using weighted composites (of which estimand 2 in your example was a specific case with weight of 1 given to the terminal event).

Additional List of Issues
For the situation where there is a terminal event:

1. The use of the frailty model requires further justification because preference would always be given to not add unstructured variability to the model:

a. Is it impossible to explain the high variability in the frequency of rehospitalisation by means of co-variates?
b. If there have been attempts to explain this high variability, which models have been investigated?
c. Please discuss examples, where modelling of the high variability in rehospitalisation-rates has been attempted and in how far this has been successful / not successful.

2. ValHeft is not considered a useful example to discuss the application of recurrent events of worsening of heart failure for decision making. The key result in ValHeft was an increased mortality in patients on background ACE-inhibitor and beta blocker therapy (n = 1610), which was considered a robust result, and a decreased mortality in the other patients (n = 3400). Overall, this led to an apparent neutral effect in mortality in the study. The applicant is asked to comment on how such different results in subgroups in mortality can be detected if studies are designed based mainly on recurrent hospitalisation events and how such heterogeneity is accounted for in the modelling approaches.

3. Please discuss examples of clinical trials, where an analysis of rates of rehospitalisation for worsening heart-failure was helpful for decision making about the efficacy of a drug, or where results on HFH and mortality led to different conclusions. Please discuss this also in the context of an overall assessment of benefit and risks.