October 12, 2018

Qualification procedure: EMEA/H/SAB/090/1/2018

Responses to the Additional List of Issues received via email on September 21, 2018

Introduction

This preliminary response document addresses the additional questions raised by the Scientific Advice Working Party (SAWP) on 21st of September 2018, relating to the qualification procedure EMEA/H/SAB/090/1/2018 for the qualification opinion on *"Clinically interpretable treatment effect measures based on recurrent event endpoints that allow for efficient statistical analyses".*

Throughout this reply, we will refer to various documents that we have shared in previous communications related to this qualification procedure. For ease of reference, we attach these documents below and use the following indications:

[1] for the original request document which was submitted on 1st of February 2018;
[2] for the response document to the qualification opinion list of issues which was submitted on 6th of April 2018;
[3] for the response document to the additional clarification questions which was submitted on 23rd of August 2018.

Moreover, we will use the following abbreviations in line with [1]:

- CV cardiovascular;
- CVD cardiovascular death;
- HHF hospitalizations for heart failure;
- HR_{CV} hazard ratio parameter for CVD used for the data generation based on a joint frailty model;
- RR_{HHF} rate ratio parameter for recurrent HHF used for the data generation based on a joint frailty model.


[1]Request for qualification opinion o


[2]Response to List of Issues_final.pdf


[3]Response to List of Issues_August201

Question

Thanks for the latest set of results as shown in table A. Some of the results seen are not initially intuitive and for the purposes of a qualification it is considered important to understand the reasons for the various patterns seen, for example why the analytical estimand values for in table A are above 0.7 when there is no treatment effect on mortality, why they vary in the way they do with changing mortality rate, and why the values for estimand 2 are so large for the equal-weighted rate based estimand. To aid this understanding we make a request for a simplified version of table A.

In this table we would ask that it is assumed that there are no treatment discontinuations (either informative or non-informative) so patients stay on trial either until the end of follow-up or until death. Under this simplified scenario could table A be repeated, and a discussion provided explaining the values and patterns seen. Could additional HRcv scenarios, i.e. HRcv=0.666, 0.8, 1, 1.25, 1.5 be included in order to better understand trends? Could follow-up time also be varied - the current table has a fixed 3.5 year follow-up time - maybe repeated tables with 1.25 and 7 year follow-up could also be included?

Response:

We agree that simulations for settings without treatment discontinuation are helpful for the interpretation of the results presented in Table A, see [3]. The new simulations are provided in Table A* below. For ease of reference, we also include Table A.

In the simulations provided below, a joint frailty model was used, where the rate ratio parameter for recurrent HHF was fixed at RR_{HHF} = 0.7. It should be noted that RR_{HHF} is just a parameter in a specific (joint frailty) model used to simulate recurrent HHF data and it is not clear whether this parameter has a meaningful interpretation to patients, see also [2, reply to Question 2.4].

Estimand values were approximated by simulating data from 200.000 patients, and hence are subject to Monte Carlo error. The corresponding Monte Carlo standard errors (SE) were added to Table A* below to better assess the uncertainty in these approximated estimand values.

Table A: Terminal event case: True estimand values for four scenarios, as well as the treatment effect estimates based on five established approaches. Simulated data for 100.000 patients are generated with $RR_{HHF} = 0.7$, $HR_{CV} = 0.8; 1.0; 1.25$.

	Exposure-weighted rate based estimand*			Equal-weighted rate based estimand			Method	Estimates		
HR_{CV}	0.8	1.0	1.25	0.8	1.0	1.25		0.8	1.0	1.25
Scenario 1: Non-informative HHF	0.783	0.722	0.688	0.752	0.727	0.72	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 HHF	0.770	0.728	0.686	0.745	0.794	0.728	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 HHF+CVD	0.809	0.806	0.822	0.93	1.759	3.737	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 HHF+CVD	0.800	0.800	0.820	0.799	1.498	1.737	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 the original request document, this estimand was called Estimand 1 (HHF) and Estimand 2 (HHF+CVD), respectively.

Table A*: Terminal event case: Approximated estimand values as well as Monte Carlo standard errors (SE) under 30 scenarios. Simulated data for 200.000 patients are generated with $RR_{HHF} = 0.7$, $HR_{CV} = 0.67; 0.8; 1.0; 1.25; 1.5$.

Endpoint	Follow-up time	HR_{CV}	Exposure-weighted rate based estimand (SE)	Equal-weighted rate based estimand (SE)
HHF	1.25	0.67	0.721(0.012)	0.703(0.013)
		0.80	0.713(0.012)	0.706(0.013)
		1.00	0.680(0.011)	0.699(0.017)
		1.25	0.690(0.011)	0.703(0.014)
		1.50	0.669(0.011)	0.703(0.015)
	3.5	0.67	0.783(0.010)	0.730(0.014)
		0.80	0.718(0.010)	0.679(0.013)
		1.00	0.704(0.009)	0.700(0.013)
		1.25	0.653(0.009)	0.682(0.013)
		1.50	0.625(0.008)	0.708(0.014)
	7	0.67	0.809(0.010)	0.698(0.015)
		0.80	0.776(0.009)	0.716(0.012)
		1.00	0.700(0.009)	0.694(0.013)
		1.25	0.642(0.008)	0.707(0.013)
		1.50	0.586(0.007)	0.708(0.013)
HHF+CVD	1.25	0.67	0.711(0.010)	0.689(0.097)
		0.80	0.742(0.010)	0.948(0.250)
		1.00	0.766(0.010)	1.099(0.167)
		1.25	0.834(0.011)	0.666(0.240)
		1.50	0.866(0.011)	3.240(2.218)
	3.5	0.67	0.764(0.009)	0.239(0.123)
		0.80	0.749(0.008)	0.856(0.103)
		1.00	0.783(0.009)	0.405(0.229)
		1.25	0.797(0.009)	1.653(0.847)
		1.50	0.816(0.009)	1.361(0.282)
	7	0.67	0.791(0.008)	0.697(0.078)
		0.80	0.797(0.008)	0.995(0.322)
		1.00	0.784(0.008)	1.621(0.630)
		1.25	0.786(0.008)	1.106(0.225)
		1.50	0.781(0.008)	1.099(0.137)

We now discuss the patterns seen in Table A*, first for rate based estimands which focus on the HHF endpoint, and second for rate based estimands which focus on the composite endpoint (HHF+CVD).

Estimands on HHF

Table A* shows that both the exposure-weighted and the equal-weighted rate based estimand have an estimand value of about 0.7, corresponding to the value of the parameter RR_{HHF} in the joint frailty model, when there is no treatment effect on CVD (HR_{CV}=1) and no treatment discontinuation. For the exposure-weighted rate based estimand, the estimand value can also be derived analytically (rather than by simulation), and gives an exact value of 0.7 in this setting, see [1, Section E.3.2]. As seen in Table A, estimand values are larger than 0.7 in case of treatment discontinuation. This is expected since a patient who discontinues from an effective treatment loses the beneficial effect, and hence the treatment effect is attenuated.

Table A* also shows that if there is a treatment effect on CVD, the values for the equal-weighted rate based estimand are still close to 0.7 for all considered study durations and treatment effects on CVD. In other words, this estimand is not affected by different treatment effects on CVD. However, it is unclear whether this holds in general and whether the model parameter of a joint frailty model itself is a meaningful quantity for a patient, see [2, response to Question 2.4].

As seen in Table A*, the exposure-weighted rate based estimand gives estimand values below 0.7 for treatments with detrimental treatment effect on CVD. This is more pronounced the longer the follow-up times, since selection effects due to CVD are becoming increasingly pronounced. In case of positive correlation between CVD risk and HHF risk, the survivors tend to have lower HHF rates, which for $HR_{CV} > 1$ suggests an increasing treatment effect on HHF. Hence, as discussed in [1, Section 5.2.3.1.1] and [3, reply to Question 1], the exposure-weighted rate based estimand focusing on only HHF is sensitive to a potential treatment effect on CVD (positive or negative) in cases where there is a dependence between any unobserved risk factors for HHF and CVD events.

Estimands on HHF+CVD

Table A* shows that for the exposure-weighted rate based estimand on HHF+CVD, the estimand values are larger than 0.7 if there is no treatment effect on CVD. This is expected, as this composite estimand combines treatment effects on both HHF and CVD, and hence the overall effect is attenuated compared to the effect on HHF alone for all scenarios considered. If there is a worsening treatment effect on CVD, this is captured by this estimand, as estimand values are getting closer to 1. This effect is more pronounced for shorter follow-up times (1.25 to 3.5 years), and less the case for longer follow-up times (7 years). The reason is for long follow-up times, selection effects due to CVD are becoming increasingly important. In case of positive correlation between CVD risk and HHF risk, the survivors tend to have lower HHF rates, which for $HR_{CV} > 1$ suggests an increasing treatment effect on HHF. For the composite endpoint, where the treatment effects on HHF and CVD are combined and the HHF and CVD events occur at different rates, we still see estimand values that decrease with study duration.

Table A* indicates that calculation of a reliable estimand value for the equal-weighted rate based estimand on HHF+CVD is difficult, as seen by the very large Monte Carlo standard errors. Hence, interpretation of these approximated estimand values in Table A* (and Table A) remains inconclusive. This estimand appears to be very sensitive to patients who die quickly after randomization, and hence provide large event rates; see also

[3, reply to Question 1]. It should be noted that the distribution of individual HHF+CVD rates is extremely skewed. For heavily skewed distributions, the mean may not be the most appropriate summary measure. The median may also not be appropriate in this setting, as often the majority of patients have zero events. Other robust summary measures such as trimmed means could be used, however, to our knowledge experience in a clinical trial context is limited.

Estimation

The exposure-weighted rate based estimand may be estimated by the LWYY approach. In all considered scenarios, this analysis method targets the estimand (Table A, Table A*, and Table A** provided in the Appendix).

For the equal-weighted rate based estimand, none of the investigated analysis methods (LWYY, NB, WLW, PWP) targets the estimand (Table A, Table A*, Table A**). One possibility would be to use the plug-in estimator, see [3, reply to Question 1]. However, the properties of this estimator have not been investigated in the scientific literature, and it is unclear whether there are more appropriate methods for estimating the equal-weighted rate based estimand.

Summary and conclusions

The exposure-weighted rate based estimand for the composite (HHF+CVD) endpoint has the desirable property of appropriately capturing treatment effects on CVD. However this is not the case when the HHF endpoint rather than the composite (HHF+CVD) endpoint is used. The exposure-weighted rate based estimand is targeted by the LWYY estimator for all considered scenarios.

The equal-weighted rate based estimand for the HHF endpoint appears to be not affected by varying treatment effects on CVD. The interpretation of the approximated estimand values of the equal-weighted rate based estimand for the composite (HHF+CVD) endpoint remains inconclusive due to the heavily skewed distribution of the individual event rates. The meaningfulness of using the mean as a summary measure for the equal-weighted based estimand remains also debatable. In terms of estimation, the plug-in estimator targets the equal-weighted rate based estimand, but whether this estimator is appropriate for inference is an open research question.

As highlighted in [1] and [3], finding suitable estimands in chronic diseases where patients may die for disease-related reasons remains fundamentally difficult both for time-to-event and recurrent event endpoints. Our aim is to substantiate the claim that interpretable treatment effect measures based on recurrent event endpoints can be defined in a way that may be more suitable (clinically and statistically) than traditional treatment effect measures based on the first composite event only. We do not seek to recommend a specific estimand choice, but rather to discuss the value and limitations of different treatment effect measures and their associated statistical analyses.

Appendix

Table A:** Terminal event case: Treatment effect estimates as well as standard errors (SE) based on five established approaches under 30 scenarios. Simulated data for 200.000 patients are generated with $RR_{HHF} = 0.7$, $HR_{CV} = 0.67; 0.8; 1.0; 1.25; 1.5$.

Endpoint	Follow-up time	HR_{CV}	Cox(SE)	NB(SE)	LWYY(SE)	WLW(SE)	PWP(SE)
HHF	1.25	0.67	0.779(0.014)	0.713(0.016)	0.721(0.016)	0.721(0.016)	0.780(0.012)
		0.8	0.779(0.014)	0.707(0.016)	0.713(0.016)	0.715(0.016)	0.778(0.012)
		1	0.742(0.015)	0.674(0.017)	0.679(0.016)	0.679(0.016)	0.748(0.012)
		1.25	0.752(0.015)	0.689(0.017)	0.690(0.016)	0.689(0.016)	0.755(0.012)
		1.5	0.735(0.015)	0.671(0.017)	0.669(0.016)	0.666(0.016)	0.738(0.013)
	3.5	0.67	0.845(0.011)	0.748(0.014)	0.785(0.013)	0.796(0.013)	0.853(0.008)
		0.8	0.798(0.011)	0.690(0.014)	0.719(0.013)	0.734(0.013)	0.809(0.009)
		1	0.790(0.011)	0.688(0.014)	0.703(0.013)	0.722(0.013)	0.804(0.009)
		1.25	0.758(0.011)	0.647(0.014)	0.653(0.013)	0.670(0.013)	0.766(0.009)
		1.5	0.746(0.011)	0.632(0.015)	0.623(0.013)	0.646(0.013)	0.751(0.009)
	7	0.67	0.862(0.010)	0.736(0.014)	0.813(0.012)	0.832(0.011)	0.873(0.007)
		0.8	0.847(0.010)	0.721(0.014)	0.778(0.012)	0.799(0.011)	0.855(0.007)
		1	0.814(0.010)	0.671(0.014)	0.699(0.012)	0.734(0.011)	0.818(0.007)
		1.25	0.778(0.010)	0.638(0.014)	0.639(0.012)	0.679(0.011)	0.787(0.008)
		1.5	0.738(0.010)	0.600(0.015)	0.582(0.012)	0.632(0.012)	0.756(0.008)
HHF+CVD	1.25	0.67	0.763(0.012)	0.683(0.015)	0.712(0.014)	0.711(0.014)	0.766(0.011)
		0.8	0.806(0.012)	0.728(0.015)	0.742(0.014)	0.743(0.014)	0.805(0.010)
		1	0.833(0.012)	0.769(0.015)	0.766(0.013)	0.764(0.014)	0.837(0.010)
		1.25	0.912(0.012)	0.868(0.015)	0.834(0.013)	0.832(0.013)	0.908(0.010)
		1.5	0.956(0.012)	0.923(0.015)	0.865(0.013)	0.862(0.013)	0.948(0.010)
	3.5	0.67	0.817(0.009)	0.694(0.013)	0.765(0.011)	0.775(0.011)	0.829(0.007)
		0.8	0.830(0.009)	0.708(0.013)	0.750(0.011)	0.764(0.011)	0.838(0.007)
		1	0.882(0.009)	0.786(0.013)	0.783(0.011)	0.801(0.011)	0.887(0.007)
		1.25	0.933(0.009)	0.852(0.013)	0.796(0.011)	0.816(0.010)	0.928(0.007)
		1.5	0.977(0.009)	0.925(0.013)	0.814(0.011)	0.842(0.010)	0.971(0.007)
	7	0.67	0.840(0.008)	0.688(0.013)	0.795(0.010)	0.809(0.009)	0.847(0.006)
		0.8	0.870(0.008)	0.736(0.013)	0.799(0.010)	0.820(0.009)	0.875(0.006)
		1	0.916(0.008)	0.790(0.013)	0.784(0.010)	0.820(0.009)	0.909(0.006)
		1.25	0.955(0.008)	0.867(0.013)	0.783(0.010)	0.829(0.009)	0.955(0.006)
		1.5	0.993(0.008)	0.934(0.013)	0.777(0.010)	0.837(0.009)	0.992(0.006)