Sample size computation when the hazard ratio is not constant

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Standard methods of summarizing the treatment difference in a comparative, randomized clinical study with a specific event time as the primary endpoint (PE) are based on Kaplan-Meier curves, the logrank test and the hazard ratio, HR, which is assumed to be approximately constant over time. For designing the study, one usually utilizes an event-driven scheme to determine the sample size and this formulation is, often based, on the proportional hazard (PH) assumption.

We are in a setup where two candidate endpoints $\mathcal{E}_1$ and $\mathcal{E}_2$, or their composition $\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_2$, are potential PE. Assume that the PH assumption holds for $\mathcal{E}_1$ and $\mathcal{E}_2$. It can be proved that, only under estringent scenarios, the hazard ratio evaluated on $\mathcal{E}_*$ is constant. The aim of this talk is to discuss sample size determination for $\mathcal{E}_*$ under the assumption of the proportionality of the hazard ratios, HR_1 and HR_2 for the two candidate endpoints $\mathcal{E}_1$ and $\mathcal{E}_2$.

The starting point for this study is the asymptotic relative efficiency (ARE) method developed by Gómez and Lagakos (2013) to derive efficiency guidelines for deciding whether to expand a study primary endpoint from $\mathcal{E}_1$ to $\mathcal{E}_*$. The ARE compares two logrank tests, Z_1 and Z_*, to evaluate treatment differences based on $\mathcal{E}_1$ and $\mathcal{E}_*$, respectively, and, among other set of realistic assumptions, assumes constant hazard ratios, HR_1 and HR_2 for $\mathcal{E}_1$ and $\mathcal{E}_2$. Furthermore, ARE can be interpreted as the reciprocal ratio of the required sample sizes for Z_1 and Z_*, to attain the same power at the same significance level (Gómez and Gómez-Mateu, 2014).

We explore the use of the ARE as a tool at the design stage of the study to compute the required sample size if $\mathcal{E}_*$ is chosen as PE and we have anticipated constant values for HR_1 and HR_2 . We discuss the meaning of the ratio of the hazard function for $\mathcal{E}_*$ under these circumstances as well as the interpretation of the treatment contrast. We extend some of these ideas to clinical trials where the PE is a combination of two binary endpoints

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