INTERIM ANALYSIS AND TREATEMENT SELECTION IN TIME-TO-EVENT RANDOMIZED TRIALS IN RARE DISEASES ON A LONG-TERM HORIZON

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Context: In rare diseases, when traditional large trials may not be doable, we previously considered an approach based on a series of small two-arm randomized controlled trials (RCT) performed over a long research horizon. We concluded that, under reasonable assumptions, running more trials with smaller sample sizes and relaxed alpha-level outperformed, on the long term, traditional designs based on fewer but larger trials designed to achieve stringent evidence criteria. The aim of this work is to evaluate the added value of interim analyses (IA) for futility and/or efficacy, and to compare the performance of a series of two-arm RCTs with IA to a series of two-stage three-arm RCTs with treatment selection at interim.
Methods: We simulated a series of superiority RCTs over a 15-year period. We considered different disease severities, accrual rates, hypotheses of how treatments improve over time. We included within the series of two-arm RCTs an IA with different stopping rules for futility and/or efficacy. We also simulated a series of two-stage three-arm RCTs with treatment selection at the first stage. To compare the operating characteristics of the designs, we estimated the long-term relative survival benefit as the relative difference in hazard rates, at year-15 versus year-0, and the risk, defined as the probability of selecting at year-15 a treatment inferior to the initial control.
Results: Including interim analysis for futility within a series of two-arm RCTs further increases the benefit and decreases the risk as compared to a series of two-arm RCTs with no interim analysis. The added-value of IA is maximal for a relaxed alpha-level of 5% one-sided; the impact is small for more relaxed alpha-levels. The added-value of IA for efficacy was rather small. The performance of the series of two-stage three-arm RCTs was slightly better as compared to a series of two-arm RCTs with IA with the former achieving, on average, a greater gain and a better control of the risk.
Conclusion: For both series designs, we still recommend to relax the alpha-level when considering a series of trials run over a relatively long research horizon and when the supply of new treatments is large