Interim decision rule in adaptive designs with population selection

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The use of adaptive designs with population selection has spread in response to the emergence of numerous targeted therapies. We assume that the full population (F) comprises biomarker-positive (P) and biomarker-negative (N) populations categorized based on a promising biomarker in a setting in which the targeted therapy is beneficial only for P. Such a design provides an opportunity to stop recruitment for a population in mid-course when this population does not benefit from the treatment being tested. We consider a design setting in which the endpoint is of the time-to-event type [1–3]. In this context, an interim analysis is conducted in mid-course to identify whether F or only P is to continue into the subsequent stage. Thus, interim analysis can play a role in determining whether the targeted population is restricted to only P owing to futility for N or is continued as F. However, there are no well-established procedures for setting the threshold to select the population at interim. In this work, we propose a utility-based approach to setting the thresholds in an interim decision rule constructed on the basis of utility functions in the context of adaptive population selection design.

First, we consider the interim decision rule based on the upper limit of the interim hazard ratio denoted by $\widehat{HR}_g^U$ for $g \in \{F, P\}$ as follows. (i) Continue F if $\widehat{HR}_F^U < \theta_F$, regardless of the value of $\widehat{HR}_P^U$. (ii) Continue only P if $\widehat{HR}_F^U > \theta_F$ and $\widehat{HR}_P^U < \theta_P$. (iii) Stop the trial for futility if $\widehat{HR}_F^U > \theta_F$ and $\widehat{HR}_P^U > \theta_P$, where θ_g denotes the threshold of the hazard ratio for $g \in \{F, P\}$ at interim. Second, we use the predictive power $\widehat{PP}_g$ for $g \in \{F, P\}$ in the interim decision rule as follows. (i) Continue F if $\widehat{PP}_F > \pi_F$, regardless of the value of $\widehat{PP}_P$. (ii) Continue only P if $\widehat{PP}_F < \pi_F$ and $\widehat{PP}_P > \pi_P$. (iii) Stop the trial for futility if $\widehat{PP}_F < \pi_F$ and $\widehat{PP}_P < \pi_P$, where π_g denotes the threshold of predictive power for $g \in \{F, P\}$. We assume that the utility function is constructed on the basis of pseudo clinical trial results via simulation. Then, the optimal thresholds θ_g and π_g for $g \in \{F, P\}$ are explored via grid search to maximize the utility function.

This talk discusses the adaptive population selection designs with the interim decision rule using the proposed approach.

References

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