

Interim Decisions with Time-to-Event Endpoints under Non-proportionality of Hazards

Author: Rajat Mukherjee

In classical adaptive designs of RCTs with time-to-event (TTE) endpoints the conditional power (CP) is routinely used for making interim decisions such as sample size re-estimation, dose selection, population enrichment, etc. This CP is calculated under the assumption of constant and proportional hazard rates. Under non-proportionality and/or time dependent hazard, the CP can easily mis-inform decision makers. The use of the Bayesian predictive power (BPP) has recently gained popularity due to the flexibility in modeling as well the wholesome use of the interim data for interim decision making. However, the complexity of calculations limits its use. We discuss different approaches and simplifications for the calculation of the BPP for TTE endpoints and discuss its application in Bayesian as well as Hybrid adaptive trials. We discuss these topics while using the adaptive trial design for the PROTECT IV trial as a case study.

Keywords: Time-to-event endpoints, Non-proportional hazards, Bayesian Predictive Power, Adaptive Design, Interim decisions.