Predicting Timing for the Final Event in a Clinical Trial Using a Nonparametric Bayesian Poisson Process Simulation

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The Methodological Question Being Addressed

Continuous monitoring of event incidence rates plays a critical role in making timely decisions that affect clinical trials. It is often important to determine if initial assumptions apply to the study of interest and whether predetermined operational milestones will be met. We propose strategies for determining the timing of the final events in blinded settings.

Introduction (Aims)

The duration of time-to-event clinical trials is based on the observation of predetermined total numbers of events. Examples of such events include death, relapse, adverse drug reaction, or new disease development whose timing can only be estimated based on prior experience. Timing for events of prospectively designed trials may deviate from historical results. Therefore, for such endpoints, patient participants must be followed over a long span of time with uncertain actual timing for events. This uncertainty has many important design and operational implications, including sample size estimation, determination of when to close enrollment, and determination of resource needs.

Methods

We have developed a blinded, nonparametric Bayesian Poisson process simulation to confirm initial assumptions for determining the timing of the final events to better inform operational decisions.

Results

As a case study, we have considered data from a recently completed clinical study conducted to test the safety and efficacy of a long-acting injectable antipsychotic in patients with schizoaffective disorder. We blinded treatment assignments and applied nonparametric Bayesian Poisson process simulations to estimate the timing of the final relapse. For this approach, experts' prior knowledge about both the frequency and timing of the event occurrence was combined with observed data. Five interim analyses were conducted. These results find that the precision of credible intervals improves as more interim data become available.

Conclusions

Blinded, nonparametric Bayesian Poisson process models are shown to be superior to their parametric and/or non-Bayesian counterparts. These simulations exploit both observed and censored times to relapse for purposes of prediction. They address limitations of alternative approaches that include (1) issues associated with staggered entry, (2) failure to make proper use of information arising from censored data, (3) evolution of hazard and accrual rates, and (4) failure to provide model flexibility.

Disclosures

Ibrahim Turkoz is an employee of Janssen Research and Development, LLC, and is a Johnson & Johnson stockholder. Marc Sobel has nothing to disclose. Brianne Brown and Larry Alphs are employees of Janssen Scientific Affairs, LLC, and are Johnson & Johnson stockholders. Janssen Scientific Affairs has provided financial support for this study.