ASA-BI Statistics Webinar Series

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**Feburary 27th,
Tuesday
9-10 am EST**

For more information regarding upcoming webinar schedule, please contact: medecc.us@boehringer-ingelheim.com

Title

Dose-escalation trials without monotonicity assumption: A weighted differential entropy approach

Abstract

Methods for finding the highest dose that has an acceptable risk of toxicity in Phase I dose-escalation clinical trials assuming a monotonic dose-response relationship have been studied extensively in recent decades. The assumption of monotonicity is fundamental in these methods. As a result, such designs fail to identify the correct dose when the dose-response relationship is non-monotonic. Moreover, many of these approaches can not be straightforwardly extended to dose-escalation studies of drug combination because ordering the dose combinations is difficult.

We propose a dose-escalation method that does not require monotonicity or any pre-specified relationship between dose levels. The method is motivated by the concept of the weighted differential entropy. For a given weight function the asymptotically unbiased and consistent estimator of the proposed dose escalation criterion is found. For small sample size, it is shown in simulations that the proposed method is comparable to well-studied methods under the assumption of monotonicity and outperforms them when this assumption is violated. We subsequently extended the method to limit the risk of overdosing by imposing the time-varying safety constraint. Again simulations are used to show good performance under many different scenarios.

Professional Biography

Dr. Jaki is professor of Statistics at Lancaster University and director of the Medical and Pharmaceutical research unit (www.mps-research.com). He is an NIHR senior research fellow, coordinator of the EU funded IDEAS network (www.ideas-itn.eu) and a co-investigator of the MRC's North-West Hub for Trials Methodology Research.

His methodological research has focused on adaptive designs and multiplicity, Bayesian methods and estimation with sparse data. He has worked on estimators for PK parameters, developed adaptive designs, and investigated Bayesian methods for dose-escalation.

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- American Statistical Association (Boston, Connecticut, Florida, New Jersey, Princeton/Trenton, and Washington chapters)
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