Adaptive experimental design for optimum dose-finding in Phase I clinical trials

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Abstract

Generalized Linear Models (GLM) are an intermediate form between Linear and Non-linear Models and so this talk will, we trust, be appropriate for the LinStat conference. We present an application of a GLM in drug development studies.

The maximum tolerable dose in Phase I clinical trials may not only carry too much unnecessary risk for patients but may also not be the most efficacious level. This may occur when the efficacy of the drug is unimodal rather than increasing, while the toxicity will be an increasing function of the dose. It may be more beneficial to design a trial so that doses around the so-called Biologically Optimum Dose (BOD) are used more than other dose levels.

Zhang at al (2006) presented simulation results for an adaptive design for a variety of models when the response is trinomial ("no response","success" and "toxicity"). The choice of dose for the next cohort depends on the information gathered from previous cohorts, which provides an updated estimate of BOD for the next experiment. However, this reasonable approach is confined to a sparse grid of dose levels which may be far from the "true" BOD.

In our work we explore the scenarios used by Zhang but search for the BOD over a continuous dose interval. This increases the percentage of patients treated with a good approximation to the "true" BOD. However, more patients may be treated at a high toxicity probability level and so some further restrictions are introduced to increase the safety of the trial. We give examples of the properties of various design strategies and suggest future developments.

Keywords

Generalized Linear Models, Biologically Optimum Dose, Efficacy and Toxicity.

References

Zhang, W., D.J. Sargent, and S. Mandrekar (2006). An adaptive dose-finding design incorporating both toxicity and efficacy. *Statistics in Medicine 25*, 2365–2383.