CONTINUAL REASSESSMENT METHOD FOR LONGITUDINAL BINARY DATA

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In this communication, we propose a dose finding method extending the Continual Reassessment Method (CRM) for longitudinal data with intra-patient dose (de)escalation. Our method is motivated by clinical trials of targeted agents administered orally as chronic treatment until disease progression. In this trial, increasing dose-toxicity and dose-efficacy relations are expected.

The outcome of interest is the toxicity recoded as a binary variable repeatedly measured after each cycle of treatment. In addition to the Maximum Tolerated Dose (MTD), we introduce the individual MTD, associated with a given percentile of the individual dose-toxicity relation. After each cycle, dose allocation is reassessed and patients are recommended the dose whose estimated probability of toxicity is closest to θ; this "individual MTD" is assumed to give the best chance of treatment benefit. An individual model of the dose toxicity relation is constructed, as well as a marginal model. Following CRM principle, we rely on a simple under-parameterized "working models".

In a simulation study, we investigate the operating characteristics of this method under model misspecification. We show the impact of disease progression on estimates of the MTD and its relation to the sample size. We finally present a retrospective analysis of a trial investigating a targeted agent against glioma.