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Editorial

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Model Based vs. Rule Based Designs in Phase I Dose Finding Clinical Trials

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A phase I clinical trial is needed when a new drug or treatment is first used in human subjects. For ethnic reason, in such a trial, we have to carefully balance the possible benefit and harm so that the benefit is maximized and harm is minimized, which deems that the design is adaptive with small sample size, and is primarily focusing on safety end-points with efficacy end-points as secondary ones.

Various adaptive designs have been developed to find a Maximum Tolerant Dose (MTD) with acceptable Dose Limiting Toxicity (DLT) rate pre-defined by investigators. Such designs can be grouped into rule-based designs and model-based designs. The widely used rule-based design is the 3+3 design[1] whereas the most referenced model based design is Continuous Reassessment Method (CRM).[2] In a 3+3 design, dose escalation or de-escalation depends on the toxicity of current dose through assigning group of 3 patients to a dose. It follows an up and down algorithm or a random walk rule according to which we choose dose adaptively based on toxicity. Namely, if the toxicity in current dose is too toxic, we lower the dose; if no unacceptable toxicity occurs in current dose, we can choose stay on the current dose or escalate to a higher dose. Lin and Shih[3] extend the 3+3 design to a generalized form called A+B designs where A and B can be other numbers other than three. Other rule based designs following the same up and down algorithm are based on other statistics. For example, an isotonic design bases on isotonic estimate of toxicity instead of raw toxicity with assumption that the toxicity increases with dose increasing.[4] A t-statistics design[5] bases on t-statistics whereas modified Toxicity Probability Design (mTPI) bases on toxicity probability interval.[6] CRM is a model-based method to estimate the dose-toxicity curve and to assign patients at a level closest to the current estimate of maximum tolerant dose (MTD). The variations of CRM are modifications of CRM in different ways. For example, there are three models such as tangent, power and logistic model used in CRM. Two often used statistical estimators for CRM are Bayesian approach and Maximum Likelihood (ML). In Escalating with overdose control (EWOC) design,[7] CRM is modified with a Bayesian loss function to deal with overdose toxicity whereas in Time To Event CRM (TITE-CRM)[8] a weight (e.g., the proportion of time in the study) is assigned in the likelihood to deal with delayed toxicity when the observation time is long.

Many investigators prefer the traditional 3+3 design and its variations as they consider such designs are "safer" given the fact that they have been most often used. For example, Rogatko et al[9] found that there are 1,215 articles (98.4%) with the 3+3 design or its variations being reported whereas only 20 articles (1.6%) with CRM or its variation being reported out of 1,235 papers published in 116 journals from 1991 to 2006. As a matter of fact, the results of simulation studies have shown that the 3+3 design is not necessarily safer than CRM designs.[10] In the review of 53 published phase I trials by Iansonos and O'Quigley,[11] CRM is shown to be safe as well. Perhaps, the main reason for the popularity of the traditional 3+3 design is probably because of its simplicity and easiness of understanding and application. However, a key drawback of the 3+3 design is its slow convergence to the target dose or the doses near target. In contrast, CRM designs show a quicker convergence to the target dose or the doses near target. However, CRM designs usually are more difficult to understand and apply.

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We would expect that more investigators would be interested in using the model based designs in their Phase I clinical trials if an easy to use software is available for application of CRM. Although interactive adaptive designs for Phase I clinical trials have been included in software such as EAST, the software is not free. We have developed a user-friendly utility program in R to implement different model-based adaptive designs, as well as the rule-based designs, with simulation and dose calculation function, for clinical trial Phase I. The program is free to download at https://apps2.ctsicn.org/~ywang/interface.php.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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