Extending the Time-to-Event Continual Reassessment Method to Handle Patient Heterogeneity

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The presence of patient heterogeneity in dose finding studies is inherent. When not accounted for in the trial design, some subjects may be exposed to toxic or inefficient doses. An option for handling patient heterogeneity is to conduct separate trials; however factors such as cost or lack of resources limit its feasibility. Extending current dose finding designs to handle the patient heterogeneity maximizes the utility of existing methods within a single trial. We propose a modification to the time-to-event continual reassessment method (TITE-CRM) to handle two groups by using a two-parameter model and maximum likelihood estimation (MLE) method. We derive the estimating equations and use numerical methods to obtain solutions. The general form of the estimating equations provided allows for the method to be customized (i.e. dose-toxicity function, weight, group relationship) and for separate group maximum tolerated dose (MTD) to be recommended. The finite sample properties of the design including bias, variance and the estimation of the MTD are investigated. The effect of group allocation is considered with the one-sample TITE-CRM used for comparison. Additionally, the estimation resulting from assuming two groups need to be accommodated when in fact the sample is homogenous is considered. As expected for MLEs, some bias for the parameter estimates exists. Caution should be taken when using the method with large group imbalance as the likelihood estimates are often unstable and unreliable. Due to the sequential nature of the trial, the recruitment of each group can be monitored and the imbalance addressed by increasing the representation of a group in the sample with a focused approach. In general, the two-group TITE-CRM finds the MTD for each group and does so in a single trial which is especially beneficial when resources are limited.

*Joint work with Inmaculada Aban