Continual reassessment method adaptively changing the prior distribution referring to initial cohort observation

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Phase I study in Oncology used continual reassessment method (CRM) are increasing. In a sense of non-informative prior, any vague prior distributions of model parameter are employed, because of no prior information about the new agent or treatment. However, there would be any available information prior to the study if the drug has already been tested in other country. If investigators are interested in a combination therapy setting, each drug must have been tested in different trials. So that it is natural to elicit narrower prior distribution which reflects their belief of (un)certainty based on their available information. Most investigators are also conservative and prudent to decide the starting dose level of the study so as to employ sufficiently safe dose and two or three higher dose levels which would be closed to the target are planed to be administrated.

If dose limiting toxicity (DLT) is observed in the initial cohort of “sufficiently safe starting dose”, investigators would doubt that their prior belief would be true, and cannot distinguish either by chance or that their prior estimate about DLT occurrence probability is lower than the true. If it’s latter case, the false prior distribution will lead to overestimate of maximum tolerated dose (MTD) and increasing patients who are treated with higher dose levels.

To solve this issue, we propose the CRM considered possibility of underestimation of DLT occurrence probability. Our method allows adaptively changing the prior distribution referring to initial cohort observation. From the observed toxic response, if the probability of underestimation is low, the study is continued without any change. If the probability of underestimation is high, we change the prior distribution to be non-informative as a result of decreasing investigators’ degree of certainty. We also need more patients until investigators gain enough belief.

We compared proposed method with ordinal CRM by simulation study. According to the results, our method offers robustness about the false prior information with slight decrease of efficiency.