ABSTRACT

Dose escalation trials play a critical role in determining the dose-toxicity relationship and the maximum tolerated dose (MTD) of a therapeutic agent as well as optimizing the dosing schedule while ensuring patient safety. This thesis investigates various modeling approaches for dose escalation trials under the change of the dosing schedule, with a focus on Bayesian logistic regression models (BLRM). Three different approaches for modeling the dose-toxicity relationship under the change of the dosing schedule are examined, differing in the type of incorporating the patient observations from the initial schedule, including a robust meta-analytical predictive (RMAP) approach as well as using an indicator variable as additional covariate in the BLRM.

Using simulation studies, this thesis compares these approaches in terms of patient enrollment, occurrence of dose-limiting toxicities (DLTs), accuracy in MTD estimation, and MTD overestimation. Notably, the scenarios were simulated to systematically explore the performance of each approach under different conditions, providing insights into their relative strengths and limitations.

The findings reveal a conservative nature of the RMAP approach, which prioritizes patient safety by selecting lower dose levels as MTDs. However, the accuracy of MTD estimation is influenced by the steepness of the true toxicity curve and the selected dose levels. Despite its conservatism, the RMAP approach demonstrates favorable outcomes in terms of patient safety, resulting in fewer DLTs and reduced exposure to toxic doses while mitigating MTD overestimation.

Future research directions include adapting the RMAP approach to incorporate efficacy alongside safety, optimizing weighting factors for borrowing strength from the initial schedule data within the RMAP approach and exploring meta-analytic combined (MAC) approaches for dose escalation modeling after change of the dosing schedule. By addressing these research directions, the efficiency, safety, and effectiveness of dose escalation trials in clinical practice can be enhanced.