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Editorial
Dose Finding and Related Topics in Drug Development

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1. INTRODUCTION

Dose finding in drug development remains an enduring and captivating topic that statisticians love and wrestle with. On one hand, it brims with promise and abundant opportunities for innovative statistical applications; on the other, its practical implementation is often constrained by ethical considerations, limited patient populations, and operational feasibility challenges. The field continues to motivate statisticians because of this dynamic blend of theoretical creativity and high-stakes practical impact, where methodological advances directly influence patient outcomes and therapeutic success.

Nevertheless, the immense potential in this field has inspired generations of statisticians to develop superior methods aimed at enhancing efficiency, minimizing risks, and optimizing dose selection throughout the drug development process. Dose finding can arise across multiple phases of drug development. In phase I trials, a common goal is to characterize the safety and pharmacological profile of a new drug. In oncology in particular, dose finding is often through dose-escalation studies and has traditionally focused on identifying a maximum tolerated dose. In phase II trials, the emphasis typically shifts from safety to efficacy, with dose finding aimed at characterizing the dose-response relationship and identifying a minimum effective dose to carry forward into larger phase III studies. This classical phase-based framework has evolved substantially in recent years. Regulatory initiatives such as the U.S. Food and Drug Administration's Project Optimus have further accelerated this shift, particularly in oncology, by advocating dose optimization based on the overall benefit-risk profile rather than dose escalation to maximal tolerability. This paradigm has given rise to dose-optimization trials, potentially conducted in a seamless phase I/II fashion, with the goal of identifying an optimal biological dose that jointly accounts for toxicity, efficacy, and other clinically relevant factors. Contemporary dose-finding designs increasingly integrate diverse sources of information, including pharmacokinetics and pharmacodynamics, biomarkers, patient-reported outcomes, real-world evidence, and historical data, reflecting a broader and more holistic approach to dose selection in modern drug development.

This special issue is motivated by the methodological evolution and expanding scope of dose finding in drug development, together with the "Dose Finding and Other Topics in Drug Development" Conference held in 2023 at the University of Connecticut honouring Dr. Naitee Ting's contributions to this field, in which all guest editors and many contributors to this special issue participated. The collected articles showcase a diverse range of innovative and creative work, spanning general considerations in dose-finding designs [4], phase I dose-escalation and dose-proportionality studies [3, 2, 7], phase II dose-optimization and dose-response studies [6, 1], as well as contributions addressing other aspects of drug development [5]. We hope this collection not only highlights cutting-edge methodological advances, but also fosters continued dialogue and collaboration among statisticians, clinicians, and regulators to further refine dose-finding practices for the benefit of patients worldwide.

2. RESEARCH ARTICLES

[4] **Risks in Finding Doses for a New Drug.** Dr. Naitee Ting is a highly experienced statistical researcher with deep expertise in dose-finding studies in drug development. He has authored several well-regarded books on dose finding and has provided valuable insights into trial design and statistical analysis for dose-finding studies. In this paper, Dr. Ting focuses on an often-overlooked aspect of dose-finding study design: the underlying assumptions that many researchers are unaware of or fail to consider. He presents a comprehensive set of risks associated with these assumptions and offers practical recommendations to mitigate them in the design of dose-finding clinical trials. This paper serves as an essential resource to consult when planning a dose-finding study.

[3] **Up-and-Down: The Most Popular, Most Reliable, and Most Overlooked Dose-Finding Design.** The authors provide a comprehensive review of up-and-down designs (UDDs) for dose finding, a class of methods defined by a few simple rules that generate a random walk

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around a target percentile. The paper discusses both the operational mechanics of UDDs and practical estimation techniques for identifying the target dose at the conclusion of a trial. Through simulation studies, the authors demonstrate that UDDs perform competitively with, and often exhibit superior robustness compared to, more complex "Aim-for-Target" designs such as the Continual Reassessment Method and the Bayesian Optimal Interval design. Given the dominance of "Aim-for-Target" approaches in the statistical dose-finding literature, this paper offers new insight into an important yet underappreciated class of dose-finding methods, helping to fill a notable gap in methodological awareness.

[2] **Shift Models for Dose-Finding in Ordered Groups with Late-Onset Toxicity.** The authors develop a hybrid design for phase I oncology trials, termed Shift TITE-CRM, which combines elements of the time-to-event continual reassessment method (TITE-CRM) with a shift model framework to simultaneously accommodate patient heterogeneity and late-onset toxicity. Through comprehensive simulation studies, the operating characteristics of the proposed design are evaluated and compared with existing methods, demonstrating favourable performance in terms of accurately selecting the maximum tolerated dose within each patient group. To facilitate practical implementation, the authors also provide an accompanying R package that enables investigators to apply the proposed method and obtain group-specific MTD recommendations in real-world trial settings.

[7] **Bayesian Information Sharing and Interim Efficacy Monitoring for Equivalence Testing with an Application to Dose Proportionality Studies.** The authors develop a novel Bayesian approach for improving the efficiency of pharmacokinetics (PK) dose proportionality studies by incorporating interim efficacy monitoring and information borrowing from past PK studies. Building on the multisource exchangeability model (MEM), the paper extends this framework to correlated data settings arising from crossover study designs and adapts it to equivalence testing for dose proportionality through linear mixed-effects regression models. Through simulation studies, the authors demonstrate that, when the supplementary study is exchangeable with the current study, borrowing information via MEM improves estimation precision and statistical power while reducing trial duration relative to standard group sequential approaches without information sharing.

[6] **Two-Stage Design Sample Size Determination for Two Doses in Oncology Phase II Trials.** In response to the FDA's 2022 guidance on dose optimization (Project Optimus), the authors propose an extension of Simon's two-stage design for Phase Ib/II oncology clinical trials to evaluate two doses simultaneously. This method retains the option for early termination due to insufficient antitumor activity (futility), while introducing a new option for early termination based on overwhelming efficacy success. The proposed approach derives optimal decision rules and sample sizes that minimize expected or overall sample size while controlling Type I error and achieving the desired power.

[1] **LiMAP-Curvature: A Simple Model-Free Approach for Analysing Dose-Finding Studies.** In this paper, the authors introduce LiMAP-curvature (Local Maximum A Posteriori with Curvature prior), a Bayesian, model-free statistical method for detecting dose-response signals in Phase II dose-finding trials. It addresses limitations of the MCP-Mod (Multiple Comparison Procedure-Modelling) approach, which requires pre-specifying candidate dose-response models and parameters—potentially leading to poor performance if those are misspecified. LiMAP-curvature uses a Bayesian hierarchical framework that incorporates prior information on the total curvature of the dose-response curve (via a curvature parameter τ) without assuming any specific parametric form.

[5] **Three-Outcome Dual-Criterion Randomized Phase II Clinical Trial Design.** The authors propose a novel design for randomized phase II trials with binary efficacy endpoints. The design is built on a three-outcome dual-criterion framework that considers both statistical significance and clinical relevance and incorporates an inconclusive region that allows investigators to defer definitive go/no-go decisions when evidence is borderline. Both one-stage and two-stage designs are considered, where the two-stage design includes early stopping rules when there is insufficient evidence of efficacy. Under this setup, sample size determination is guided by desirable error-rate control, constraints on the inconclusive region probabilities, along with a loss function that balances sample size and power. Through simulation studies, the authors demonstrate that the proposed design achieves meaningful sample size savings and reduced type II error rates compared to existing methods.

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