Patient-Centric Pragmatic Trials: Opening the DOOR to Benefit: Risk-Based Evaluation

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ABSTRACT

Randomized clinical trials are considered the gold standard for evaluating the benefits and harms of therapeutic interventions. However, they often fall short in providing the evidence needed to meaningfully inform clinical decision-making. A major reason is the failure to identify and prioritize the most clinically relevant questions to be addressed through the trial. Traditional approaches frequently overlook these questions, leading to study designs, monitoring plans, analyses, and reporting that are misaligned with the actual needs of patient care. In particular, the conventional analytical practice of evaluating outcomes separately presents several limitations: it does not account for the associations or cumulative nature of multiple outcomes in individual patients; it complicates interpretation due to competing risks; it overlooks meaningful gradations in patient-centric outcomes; and it often separates efficacy and safety analyses across different populations, making benefit: risk assessment and generalizability unclear.

To address these challenges, the Desirability of Outcome Ranking (DOOR) paradigm has been developed and implemented in clinical trials and other medical research settings. The DOOR offers a patient-centric framework for trial design, data monitoring, analysis, interpretation, and reporting, with a focus on a comprehensive evaluation of the benefit–risk profile of therapeutic interventions. The paradigm shifts the emphasis toward the overall clinical desirability of outcomes for individual patients.

This presentation: (1) provides a comprehensive framework for the DOOR paradigm, covering statistical methods for the design and analysis of clinical trials, guiding principles, and a recommended statistical analysis plan (SAP), and (2) highlights key challenges in the design and analysis of clinical trials, illustrating how the DOOR approach addresses the challenges and offers practical, patient-centric solutions.

Keywords: Benefit: risk; Clinical Trials; Desirability of Outcome Ranking (DOOR); Partial credit; Patient-centric; Pragmatic trials; Rank-based Analysis

Adaptive Population Selection Designs for Clinical Trials with Multiple Endpoints

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ABSTRACT

In some clinical trial settings, there may be uncertainty about which patient populations are most likely to benefit from a new treatment. For example, a treatment may be hypothesized to be effective in a prespecified targeted subgroup—defined by demographic characteristics, genetic markers, or pathophysiological features relevant to the treatment's mechanism of action—while its benefit in the non-targeted (complementary) subgroup remains unclear.

This presentation investigates confirmatory clinical trials that allow adaptive selection of patient populations with prespecified subgroups based on unblinded interim results, and to assess the treatment effect in the selected subgroups for multiple endpoints. Specifically, enrollment may continue in the overall population or be restricted to the targeted subgroup. At the end of the trial, the treatment effect may then be evaluated in the overall population, the targeted subgroup, or both. In such settings, data collected before and after the interim analysis must be appropriately integrated to support valid inference on treatment effects, accounting for the multiple endpoints and potential adaptations.

This setting poses several methodological challenges: (1) the complexity of ensuring consistent patient population selection across multiple endpoints at an interim analysis; and (2) the need to consider multiple sources of multiplicity due to the involvement of multiple endpoints, subgroups, and analyses. We address both co-primary endpoints and hierarchically ordered endpoints (e.g., primary and secondary). Our approach builds on the closure principle, and multiple hypotheses are assessed using combination functions to test intersection hypotheses within the closed testing procedure, alongside specific test procedures and interim decision rules for co-primary and hierarchically ordered endpoints. We evaluate the performance of the proposed methodology, including power and sample size under Type I error control, through simulation studies. We illustrate these approaches with an example.

Keywords: Biomarker; Subgroup; Type I error; Interim analysis; Multiple Endpoint

Sample Size Assessment for Survival Trial Designs with Covariate-Adaptive Randomization

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ABSTRACT

Estimating the required sample size is an essential task for a clinical trial. It ensures statistical power and makes it possible to draw meaningful conclusions from the study results. Moreover, to minimize treatment imbalances within each covariate subgroup, covariate-adaptive randomization is a popular method. The aim of this study is to investigate the required sample size for covariate-adaptive randomization based on survival outcomes. We evaluate the testing performance using the calculated sample size under simple randomization, stratified permuted block randomization, and covariate-adaptive biased coin randomization. In order to provide preliminary insights into the trial's progress and potential efficacy, an interim analysis is commonly conducted.

The second aim of the study is to provide a strategy for interim analysis in covariate-adaptive randomization trials, which involves stopping the trial early based on accumulating data if one treatment arm proves to be significantly more effective or harmful than the others. We thus re-estimate the required sample size, propose a valid hypothesis testing method for interim analysis, and study the underlying theoretical properties of the testing statistics incorporating covariate-adaptive randomization. The performance of the proposed formula and interim strategy is evaluated through comprehensive simulations, including a sensitivity analysis. We also provide the R code to benefit the readers. Finally, an example is treated as a pilot studie, and we show that the proposed strategies are valid under covariate-adaptive randomization.

Keywords: Stratified permuted block randomization; Biased coin randomization; Cox model; Sensitivity analysis; Type I error rate; Power

Comparing MCP-MOD and Ordinal Linear Contrast Test in Dose Finding Clinical Trials: A Thorough Examination

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ABSTRACT

The MCPMod approach to design and analyze Phase II clinical trials was first introduced in the early 2000 era. It has successfully revolutionized the thinking and practice in Phase II clinical development of new drugs. However, in many situations, the assumptions behind the dose-response relationship were not realistic, and in other situations, models could be misleading. There is a need to simplify the understanding and practice of Phase II clinical development programs. If monotonic dose-response relationship can be assumed, then the ordinal linear contrast test (OLCT) approach introduced in 2017 can be considered as an improvement of MCPMod. One important contribution in OLCT is that it is easy to communicate with non-statisticians. This property largely improved the quality of teamwork in project teams and trial teams.

Keywords: Dose Finding, Ordinal Linear Contrast Test, MCP-Mod, Phase II Clinical Trial

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Naitee published articles *in Technometrics, Statistics in Medicine, Drug Information Journal (Therapeutic Innovation and Regulatory Science), Journal of Statistical Planning and Inference, Journal of Biopharmaceutical Statistics, Biometrical Journal, Statistics and Probability Letters, Statistics in Biosciences, Statistics in Biopharmaceutical Research,* and *Journal of Statistical Computation and Simulation*. His book "*Dose Finding in Drug*

Development" was published in 2006 by Springer, and is considered as the leading reference in the field of dose response clinical trials. The book "*Fundamental Concepts for New Clinical Trialists*", co-authored with Scott Evans, was published by CRC in 2015. Another book "*Phase II Clinical Development of New Drugs*", co-authored with Chen, Ho, and Cappelleri was published in 2017 (Springer). Naitee has been an active member of both the ASA and the International Chinese Statistical Association (ICSA).

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