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Randomization-based Inference for MCP-Mod

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Lukas Pin
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Lukas Pin is a third-year Biostatistics PhD student at the MRC Biostatistics Unit, University of Cambridge, supervised by Dr. Sofía S. Villar. His research focuses on response-adaptive designs, nonparametric statistics, and randomization-based inference, with applications in clinical trials. In summer 2024, he interned with the Statistical Methodology Group at Novartis in Switzerland, contributing to innovative trial designs. Lukas earned a Master's in Statistics from Humboldt University of Berlin, where he developed a novel method for constructing confidence intervals for the Mann-Whitney effect under the guidance of Prof. Brunner and Prof. Konietschke. He also holds Bachelor's degrees in Mathematics and Economics from the University of Bonn.

Oleksandr Sverdlov
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Alex Sverdlov, PhD is a Senior Director, Statistical Scientist at Novartis. With 17 years of career in the biopharmaceutical industry, Alex has been actively involved in methodological research and applications of innovative statistical approaches in drug development. He is a co-lead of the American Statistical Association’s Randomization Working Group which aims to raise awareness of the full potential of randomization to improve the quality, validity and rigor of clinical trials. Alex has co-authored over fifty refereed articles, edited three monographs ("Modern Adaptive Randomized Clinical Trials”, “Digital Therapeutics”, and “Development of Gene Therapies”), and co-authored a book “Mathematical and Statistical Skills in the Biopharmaceutical Industry: A Pragmatic Approach”.

Frank Bretz
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Frank Bretz is a Distinguished Quantitative Research Scientist at Novartis. He has supported the methodological development in various areas of pharmaceutical statistics, including dose finding, estimands, multiple comparisons, and adaptive designs. Frank is an Adjunct Professor at the Hannover Medical School (Germany) and the Medical University Vienna (Austria). Frank is a Fellow of the American Statistical Association.

Björn Bornkamp
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Björn Bornkamp works as a Senior Director Statistical Consulting at Novartis in the Statistical Methodology group. In this role he consults and researches on topics related to dose-finding studies, subgroup analyses, Bayesian statistics as well as estimands and causal inference.

Single topic, multi-speaker session, Workshop or Single presentation submission

A single topic, mutli-speaker session/workshop

Single presentation or poster submission

Dose selection is critical in pharmaceutical drug development, as it directly impacts therapeutic efficacy and patient safety of a drug. The Generalized Multiple Comparison

Procedures and Modeling (MCP-Mod) approach is commonly used in Phase II trials for testing and estimation of dose-response relationships. However, its effectiveness in small sample sizes, particularly with binary endpoints, is hindered by issues like complete separation in logistic regression, leading to non-existence of estimates. Motivated by an actual clinical trial using the MCP-Mod approach, we present penalized maximum likelihood estimation (MLE) and randomization-based inference techniques to address these challenges. Randomization-based inference allows for exact finite sample inference, while population-based inference for MCP-Mod typically relies on asymptotic approximations. Simulation studies demonstrate that randomization-based tests can enhance statistical power in small to medium-sized samples while maintaining control over type-I error rates, even in the presence of time trends. Our results show that residual-based randomization tests using penalized MLEs not only improve computational efficiency but also outperform standard randomization-based methods, making them an adequate choice for dose-finding analyses within the MCP-Mod framework. Additionally, we apply these methods to pharmacometric settings, demonstrating their effectiveness in such scenarios. The presented results underscore the potential of randomization-based inference for the analysis of dose-finding trials, particularly in small sample contexts.