Please join the Biometric Colloquium

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CHALLENGES IN RARE DISEASE CLINICAL TRIALS: RANDOMIZATION, BIAS AND STATISTICAL INFERENCE

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Rektoratsgebäude, Ebene 02+03
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Host: Nico Bruder

Abstract:

Clinical trials in rare diseases face distinct methodological challenges, primarily due to small sample sizes, heterogeneous patient populations, and limited understanding of the natural history course of the disease. As a result, existing evidence is sparse, and approximately 95% of patients affected by one of the nearly 7,000 identified rare diseases suffer from a lack of effective treatment options. Improving the design and analysis of clinical trials in this setting is therefore essential for enabling robust evaluation of new therapies.

Randomization is widely regarded as the gold standard for protecting against bias and ensuring the validity of statistical inference. However, randomization becomes more challenging to implement in complex trial settings, particularly in adaptive designs, as well as in studies with multiple endpoints. In rare disease trials, where blinding is often limited, allocation bias represents a central concern. Allocation bias arises when future treatment assignments can be predicted based on prior allocations, potentially leading to the preferential assignment of patients with specific characteristics to treatment arms. In addition, other sources of bias, e.g. chronological bias, may emerge, particularly in complex designs such as platform trials. We examine the impact of these biases on statistical inference across various clinical trial designs, including platform trials and multiple-endpoint settings. By employing direct measures such as the mean actual Type I error probability, mean actual power and the go-no-go criterion, we quantify these effects and provide guidance on selecting randomization procedures that minimize the trial's susceptibility to bias.

Statistical inference in rare disease trials is further complicated by small sample sizes and patient heterogeneity. In particular, for binary outcomes, standard large-sample methods may perform poorly due to low power and unreliable asymptotic approximations. In this context, a novel exact stratified test based on Boschloo's test is introduced and compared with existing approaches, including the (stratified) Fisher's exact test, Boschloo's unconditional exact test, and the Cochran–Mantel–Haenszel

test. The results demonstrate that tailored testing strategies can improve power while maintaining control of the type I error rate.
Overall, these findings highlight the need for carefully chosen randomization strategies to reduce susceptibility to bias, alongside adapted statistical methodologies to ensure valid inference in rare disease clinical trials. Such approaches are critical for generating reliable evidence and ultimately improving treatment options for patients with rare diseases.

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