

“Crossover Trial Designs for Absorbing Binary Endpoints”

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The crossover is a popular and efficient trial design used in the context of patient heterogeneity to assess the effect of treatments that act relatively quickly and whose benefit disappears with discontinuation. Each patient can serve as her own control as within-individual treatment and placebo responses are compared.

Conventional wisdom is that these designs are not appropriate for absorbing binary endpoints, such as death or HIV infection. We explore the use of crossover designs with an absorbing binary endpoint and show that they can be more efficient than the standard parallel group design when there is heterogeneity in individuals' risks. We also introduce a new two-period design where first period survivors are re-randomized for the second period. This design combines the crossover design with the parallel design and achieves some of the efficiency advantages of the crossover design while ensuring that the second period groups are comparable by randomization. We discuss the validity of the new designs and evaluate both a mixture model and a modified Mantel-Haenszel test for inference. Simulations are used to compare the different designs and an example is provided to explore practical issues in implementation.