RANDOMIZED DISCONTINUATION TRIALS WITH BINARY RESPONSES: DESIGN AND ANALYSIS

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Randomized Discontinuation Trials (RDT) are usually two phase designs and become rather popular across a number of therapeutic areas (oncology is one of the most known) . A single arm trial, called open phase (phase I), is followed by a randomized blinded two-arm trial (phase II) to compare two treatments (generally one needs to be placebo). Intuition and numerous simulation exercises show that RDT may potentially increase a sensitivity of trials relatively to the traditional patient allocations. This increase can be substantial if the open phase provides a reliable separation of the population into two subpopulations: responders and non-responders. We compared RDT (analytically and numerically) with the traditional two-arm randomized clinical trial (RCT) when the outcomes are binary and the population of interest consists of three groups, placebo responders, treatment responders and non-responders. The results are derived in the "parameter estimation" setting and are based on comparing variances of maximum likelihood estimators for different designs. We identify conditions under which RDT is superior to RCT. They include the response rates, misclassification rates and randomization strategy at the second stage. Transition to hypothesis testing is shortly discussed and is rather straightforward in the asymptotical setting.