

Design considerations in **clinical trials** with adaptive stopping, arm-dropping and randomisation

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Conclusion

Trials using adaptive stopping, arm-dropping and randomisation strategies require thorough planning and methodological knowhow. In this overview, we have outlined 7 key decisions pertaining to their design and crafted freely available software to facilitate this process, enabling fellow trialists to hit the ground running when embarking on this endeavour. In theory, one could consider myriad trial designs but focusing on select meaningful designs and iteratively submitting them to simulation-based comparison likely suffice to select a prudent and performant design.

Introduction

Conventional randomised clinical trials are inflexible and risk running longer than needed or turning out inconclusive, especially if sample sizes rely on inflated expectations, as is common. Adaptive clinical trials may remedy this by increasing trial efficiency and the chance of allocating participants to more promising interventions.

Objectives

To provide guidance on key decisions pertaining to planning adaptive clinical trials with adaptive stopping, adaptive arm dropping and/or response-adaptive randomisation (RAR).

Methods

We built and used adaptr (R package available on CRAN; see inceptdk.github.io/adaptr) and ran 10,000 simulations for each of 3 scenarios (no, large and unimportant effects), each with a 4-arm, binary-outcome trial and maximum 10,000 participants.

Results

We identified 7 key methodological decisions of composite nature. #1: Decide on appropriate interventions and, if relevant, specify the common control. #2: Choose an apt outcome and the statistical model to guide and underpin adaptive analyses; consider follow-up duration and expected data completeness. #3: Decide on timing and frequency of adaptive analyses; consider using a burn-in period without adaptations to prevent undue influence of random fluctuations. #4: Define trial-stopping and arm-dropping rules: when to consider an arm superior, inferior, practically equivalent, or futile to the control or (for all but futility) all other arms. #5: Set up the initial allocation scheme (e.g. equal allocation in the absence of a control arm) and randomisation scheme (e.g. fixed, RAR in all arms, or RAR in non-control arms); decide whether to tailor randomisation for the control arm (e.g. matching allocation probability with the best-performing arm). #6: Choose appropriate performance metrics, e.g. total sample size required to stop the trial, probability of conclusiveness (power) and ideal design percentage. The choice involves a trade-off considering logistics, economic constraints, and weighing benefits of enrolled (internal) against those of future (external) patients. #7: Devise realistic scenarios with reasonable outcome values (e.g. event rates for binary outcomes) in each arm and report pertinent results prior to trial initiation. Use a *null* scenario to estimate the risk of type-1 errors.

Our simulations indicated that higher control-arm allocation and RAR in non-control arms be preferable in trials with a common control; some level of restriction on RAR may strike a good balance between maximising ideal design percentage and minimising sample sizes and event counts; and different designs can perform similarly, i.e., multiple designs may be reasonable insofar as obviously inferior ones be disregarded.



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adaptr website

incept.dk