Statistical Science
2023, Vol. 38, No. 2, 216–218
https://doi.org/10.1214/23-STS865C
Main article: https://doi.org/10.1214/22-STS865

Comment: Advancing Clinical Trials with Novel Designs and Implementations

Lorenzo Trippa and Yanxun Xu

We extend our congratulations to Robertson and coauthors [12] for their comprehensive overview of response adaptive randomization (RAR) in clinical trials and insightful comparative analyses. Their contribution is noteworthy for clearly demonstrating the diversity of RAR designs and algorithms that utilize the available data to update randomization probabilities throughout the enrollment period. For instance, several forms of Bayesian RAR tend to accelerate the enrollment to the most promising arms, while other RAR strategies vary the randomization probabilities to enhance trial power compared to fixed or balanced randomization. The authors accurately highlight the wide range of statistical designs based on RAR, each with different benefits and risks compared to balanced randomization.

The significance of showing marked differences of the operating characteristics of various RAR designs lies in the fact that the views of stakeholders, including biostatisticians and clinical trial investigators, on the key aspects of RAR are often influenced by their experience with a single algorithm, a narrow subset of RAR designs explored in a publication or a few RAR clinical trials with favorable or unfavorable patient allocation. Such biases can obstruct the development of effective clinical trial designs.

Additionally, it is essential to consider the broad range of settings where RAR and adaptive trial designs can be utilized in clinical research. Context-specific evaluations of RAR designs are necessary as their advantages and disadvantages over traditional randomization vary with study-specific factors such as the expected accrual rate or the risk of time trends of the enrolled population. To fully assess the potential of RAR and adaptive trial designs, it is crucial to account for these context-specific considerations.

In our experience with adaptive platform trials [1, 5, 19], it is necessary to consider both operational/implementation complexity and potential efficiencies over fixed randomization. A relevant aspect of RAR that is often overlooked is the possibility of reducing the number of patients allocated to inferior arms. Early in the trial, data may suggest that an experimental therapy has lower efficacy compared to the control. Despite this, the experimental arm is not dropped from the study at this stage because of insufficient evidence. However, frequent interim data analyses and a preplanned mechanism, such as RAR, which allows for reducing or temporarily halting enrollment to the experimental arm until additional outcome information (e.g., survival data) becomes available, along with standard early stopping rules, can reduce the number of patients exposed to inferior treatments compared to less complex designs with fixed randomization. The RAR algorithm in a multiarm study can be customized to control the number of patients exposed to potentially inferior or toxic arms.

A Positive Perspective on the Future Use of Adaptive Trial Designs

Despite significant attention paid to RAR algorithms and adaptive trial designs in academic literature, their application in clinical trials is still limited, as noted by Robertson and colleagues. Predicting which trial designs will be implemented in the next decades is challenging, but we maintain a positive outlook on the future ability of clinical research across various areas, including oncology, to leverage the advancements in RAR designs and accelerate the development of new and effective treatments. Here, we discuss three motivations.

Collaboration-Centered Strategies for the Development of New Treatments

Our optimism is driven by the growing interest and utilization of multiarm and platform trial designs. These designs offer greater efficiency by evaluating multiple experimental treatments with a shared control arm, instead of conducting separate two-arm RCTs with similar control groups. Both multiarm trials and platform trials can employ fixed randomization or RAR. In both cases, they achieve substantial efficiency gains compared to traditional two-arm RCTs [14].

Collaboration among pharmaceutical companies, biostatisticians and other stakeholders in conducting clinical studies of multiple experimental treatments presents an

Lorenzo Trippa is Associate Professor, Dana-Farber Cancer Institute and Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115, USA (e-mail: ltrippa@jimmy.harvard.edu). Yanxun Xu is Associate Professor, Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, Maryland, USA (e-mail: yanxun.xu@jhu.edu).