CLINICAL INVESTIGATION

Adaptive Clinical Trials

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Keywords: adaptive design • adaptive dose selection • improve success rates • personalized medicine • reduce costs • uncertainty in drug development

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The greatest challenge in modern drug development is dealing with uncertainty. Uncertainty regarding the expected treatment effect, uncertainty about selection of dose with best benefit/risk profile, uncertainty about population that would most benefit from the treatment. This uncertainty impacts most important success factors for a product, such as probability of regulatory approval, differentiation and expected revenues. Additional challenges in current drug development are higher costs and prolonged product development, due to increased competition, new regulatory requirements, and payers becoming a factor. Flexibility provided by adaptive design helps better cope with these challenges. The series of articles in this special-focus collection focus on various aspects of adaptive clinical trial design, as well as discussing opportunities and challenges faced in the field.

Adaptive design allows prospectively-defined changes to the ongoing trial based on the information accumulated within that trial. It has been demonstrated by simulations and in practice that they can reduce trial costs and time in development, derisk late-stage drug development, and/or improve dose and subpopulation selection by providing better information on the safety and effectiveness of drugs and devices under investigation. Weir's piece discusses how adaptive trials can improve efficiency in drug development [1]. Parke further explains how this can provide important opportunities for biotech companies and smaller pharmaceutical companies [2].

For example, reduction in costs and development time can be accomplished by combining stages of development, or by early stopping for efficacy or futility. Investment risks at late stage of development can be reduced by incorporating a sample size reassessment at an interim analysis, or simply by incorporating stopping rules for efficacy and/or futility. Loewy discusses the potential of the 'Novel Adaptive Design' is discussed as a pivotal Phase III trial in a regulatory setting [3].

Possibly the most important contribution of adaptive design is that its flexibility improves dose selection, and selection of subpopulations defined by biomarkers or other patient characteristics. This flexibility is particularly applicable at exploratory stage of development. For example, one can start a Phase 2b trial with a larger number of doses/regiments, and drop ineffective or unsafe arms over the course of the trial while assigning more patients to better performing arms, according to a prespecified adaptive randomization algorithm. Hu is describing application of adaptive randomization to personalized medicine [4]. Additionally, adaptive designs in Phase II oncology trials are discussed by Kieser, Englert and Rauch [5], and in more detail the monitoring rules for toxicity in adaptive Phase II oncology trials are reviewed by Ivanova *et al.* [6].

Final selection of doses or subpopulations can be done even in confirmatory trials by implementing two-stage confirmatory designs with dose or subpopulation selection. Simon outlines a novel method for adaptive enrichment designs, which allow

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the simultaneous construction and use of biomarkers during an ongoing trial [7]. An example of the potential gains, from the field of Alzheimer's research, is discussed in Jaki's piece on multiarm clinical trials with treatment selection [8].

Finally, the application of simulations to optimize learning and confirmatory stage of drug development are discussed by Hummel, who argues that including simulations into adaptive trial design can assist in reducing the ever-escalating costs of drug development, and improving on very low success rates [9].

In addition to strategic and financial benefits of adaptive design, there are clear benefits for patients as well. It has been often stated that they are ethical, as they allow for early stopping of products/doses with inadequate benefit/risk profile, early filing for good ones, and they also gradually allocate more and more patients to doses with more favorable benefit/risk profile. What is, however, an even greater ethical benefit is that what goes to the market is a product with more favorable benefit/risk, or that a subpopulation that can benefit the most has been identified. This affects thousands of patients, and is the greatest ethical contribution of adaptive trials. Therefore, we can expect more widespread application of adaptive design with further emergence of the personal medicine.

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