

Designing and Implementing Adaptive Designs for Clinical Trials

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Logistical and operational considerations in designing and implementing adaptive designs have recently drawn greater attention because the infrastructure for managing traditional double-blind, randomized, parallel group clinical trial does not lend itself to the challenges presented in implementation of flexible designs. According to Krams and Quinlan: "Adaptive designs would benefit from building (1) flexibility and (2) the capability for high-speed data acquisition/analysis/reporting into the infrastructure supporting the trial".¹

The EMEA defined a trial as "adaptive" if statistical methodology allows the modification of a design element (e.g. sample-size, randomization ratio, number of treatment arms) at an interim analysis with full control of type I error.² The benefits of employing adaptive designs include acceleration of the clinical trial process, enhancement of trial efficiency, and improvements in patient safety. To achieve these benefits clinical teams must adhere to the scientific method by incorporating plans for change in the study protocol and they must implement those planned changes efficiently and effectively. Adaptive designs may have one or more of the following rules applied to the interim look at data: (1) allocation rule, (2) sampling rule, (3) stopping rule, and/or (4) decision rule.³

- (1) Planning interim efficacy evaluations with potential early stopping decision or trial extension based on established benefits;
- (2) The possibility of adding or shutting down treatment arms while the study is in progress based upon predetermined rules;
- (3) Changing the ratio of subjects to treatment group;
- (4) Changing drug cohorts; and
- (5) Adaptive randomization algorithms for maximizing balance of subject allocation.

Particular statistical challenges are encountered with each type of adaptive design and designs combining several forms. For example, dose escalation studies may have a variety of experimental designs to best suit particular therapeutic areas and experimental problems.

IVRS and EDC are enabling clinical technologies that yield real-time data used to drive adaptive decisions and enable the study changes that result from those decisions. The ability to rapidly implement adaptive decisions is directly related to the flexibility that is built into the IVRS, EDC, and drug supply management strategy before the study starts. The success of adaptive trials is closely related to careful planning, teamwork, and integration of clinical technologies.

¹ Quinlan, J.A., Krams, M. Implementing Adaptive Designs: Logistical and Operational Considerations. Drug Information Journal, 2006;40:437-444.

²EMEA Doc. Ref. CHMP/EWP/2459/02. Draft: Reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plan. 23 March, 2006. <http://www.emea.eu.int/pdfs/human/ewp/245902en.pdf>

³ Dragalin, V. Adaptive Designs: Terminology and Classification. Drug Information Journal, 2006;40:425-435.