RESPONSE ADAPTIVE RANDOMIZATION IN CLINICAL TRIALS

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Summary
Clinical trials that take into account subjects’ responses during the allocation process are being increasingly used. This chapter reviews the randomized play the winner rule and describes the statistical methodology for analyzing data resulting from these clinical trials. A newer design using the regression modeling of the outcome is also described. Several statistical challenges are outlined.

1. Introduction
Response adaptive designs have a chequered but long history of practice in clinical trials. These designs use information on participant's response to intervention during the course of a clinical trial to determine the allocation of a new participant. Examples of response adaptive randomization models include randomized play-the-winner (RPW) rule and the multi-armed bandit models. The RPW designs have been used in conducting Phase III clinical trials. Recent works have also suggested that using response adaptive designs can lead to significant increase in the number of subjects allocated to a "better performing" intervention which in some cases could lead to saving lives.

A fixed allocation procedure assigns an intervention to participants with prespecified probability, usually equal, and is unaltered during the course of the study. It is widely accepted by the scientific community that a randomized clinical trial with a fixed allocation procedure is the "gold standard" for generating scientific evidence to evaluate a set of competing interventions. However in clinical trials involving fewer patients, a fixed allocation procedure could lead to serious imbalances in the number of subjects
assigned to various interventions and thus jeopardize the validity of the statistical analysis.

Adaptive statistical designs, as the name suggests, change the allocation probabilities to interventions as the study progresses. Two kinds of adaptive designs have been discussed in the literature: (1) designs that change the allocation probabilities to the interventions depending on the imbalances in baseline characteristics or the imbalances in the number of participants in various treatment groups and (2) designs that change the allocation probabilities based on the responses of participants assigned to the intervention. This article deals with the second kind of adaptive designs. Other kinds of adaptive designs can be envisioned; for instance, designs that account for toxicity and efficacy and designs that account for balance and response. However, designing of clinical trials and statistical analysis of data resulting from these trials and their practical merits have not been well investigated in the context of Phase II/III trials.

A fair amount of statistical literature that develops methodologies for data arising from the conduct of randomized play-the-winner rule, has evolved during the past decade. A multi-center clinical trial comparing fluoxetine to placebo for depressive disorder employing an RPW rule will be discussed below. This design, apart from being response adaptive, possessed a number of subtleties. There is a wealth of statistical issues underlying these data that are not yet well understood. We will outline some of these ideas and models pertaining to these data in the present article.

The rest of the article is organized as follows: Section 2 explains the basic design and describes an example and the assumptions concerning the design, while Section 3 is devoted to developing the likelihood methods for data analysis. Section 4 deals with nonparametric methodologies, and Section 5 is devoted to some new regression models and some new designs based on regression models that account for covariates. Section 6 contains concluding remarks.

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**Biographical Sketch**

Anand Vidyashankar was born in Bombay, India. He obtained his B.Sc and M.Sc in Statistics from the University of Madras, India, and his Ph.D. in Statistics and Mathematics from Iowa State University, U.S.A. He is currently an Associate Professor at The University of Georgia, U.S.A. He has published several research papers on Probability, Statistics, and Biostatistics, and offered consultancy to several Pharmaceutical companies.