RESPONSE ADAPTIVE RANDOMIZATION IN CLINICAL TRIALS

A.N Vidyashankar
Department of Statistics, University of Georgia, Athens, GA, USA

Keywords: Play-the-Winner, Randomized Play-the-Winner, Likelihood, Hellinger Distance, Branching Processes, Polya Urns.

Contents

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 fluoxteine 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.

-
-
-

Bibliography

Anscombe F.G. (1963). Sequential medical trials. *Journal of the American Statistical Association* 58, 365-383. [This paper develops a stopping rule for assigning treatments so as to maximize the expected benefit to patients. This paper can be considered the first response adaptive design paper.]

Bandyopadhyay U. and Biswas A. (2001). Adaptive designs for normal responses with prognostic factors. *Biometrika* 88, 409--419. [This paper develops a response adaptive design that accounts for prognostic factors.]

Cheng, An-lin and Vidyashankar, A.N. (2005). Minimum Hellinger distance estimation for randomized play the winner designs, Journal of Statistical Planning and Inference

Flournoy N., Rosenberger W.F. and Wong W.K. (1997). *New Developments and Applications in Experimental Design*. Proceedings of the Joint AMS-IMS-SIAM Summer research conference held at the University of Washington, Seattle, WA, 1997, Edited by Nancy Flournoy, William F. Rosenberger and Weng Kee Wong. [This monograph contains some recent developments in adaptive designs and is edited by some of the important contributors to the field.]

Hardwick J.P. and Stout Q.F. (1995) Exact computational analyses for adaptive designs. In *Adaptive Designs*, Institute of Mathematical Statistics Lecture Notes-Monograph Series 25, Institute of Mathematical Statistics, Hayward, CA, 1995. [This paper shows how to compute optimal designs and exact analyses of allocation rules for various sequential allocation problems.]

Melfi V.F., Page C. and Geraldes M. (2001). An adaptive randomized design with application to estimation. *Canadian Journal of Statistics* 29, 107-116. [This paper proposes a simple randomized adaptive design in which the allocation of the next observation is based on the optimal proportion obtained from the data.]

Rosenberger W.F. and Hu F. (1999). Bootstrap methods for adaptive designs. *Statistics in Medicine* 18, 1757-1767. [This paper develops bootstrap methodologies for estimating the confidence intervals for the parameters of the randomized play-the-winner design.]

Rosenberger W.F. and Vidyashankar A.N. and Chopra D. (2001). Covariate-adjusted response adaptive designs for binary response. *Journal of Biopharmaceutical Statistics* 11, 227-236. [This paper develops response adaptive designs that account for covariate differences when the response is binary.]

Yao Q. and Wei L.J. (1996). Play-the-Winner for phase II/III clinical trials. *Statistics in Medicine* 15, 2413-2423. [This paper studies the randomized play-the-winner rule in the context of censored survival data and argues, using an example, that these designs can help save lives in certain situations.]

Zelen M. (1969). Play-the-Winner rule and the controlled clinical trial. *Journal of the American Statistical Association* 64, 131-146. [This paper introduces play-the-winner rule with the aim of allocating more patients to a better performing treatment in the context of clinical trials.]

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.