ELSEVIER

Journal of Economic Behavior & Organization
Vol. 66 (2008) 606–624

JOURNAL OF
Economic Behavior
& Organization

www.elsevier.com/locate/econbase

Minimizing selection bias in randomized trials: A Nash equilibrium approach to optimal randomization☆

William C. Grant[a,*], Kevin J. Anstrom[b,c]

[a] *Department of Economics, James Madison University, MSC 0204, 800 S. Main Street, Harrisonburg, VA 22807, United States*
[b] *Duke University, Department of Biostatistics and Bioinformatics, United States*
[c] *Duke University, Center for Clinical and Genetic Economics, United States*

Received 20 April 2005; accepted 7 July 2006
Available online 7 February 2007

Abstract

Randomized trials can be compromised by selection bias, particularly when enrollment is sequential and previous assignments are unmasked. In such contexts, an appropriate randomization procedure minimizes selection bias while satisfying the need for treatment balance. This paper presents optimal randomization mechanisms based on non-cooperative game theory and the statistics of selection bias. For several different clinical trial examples, we examine subgame-perfect Nash equilibrium, which dictates a probability distribution on suitable assignment sequences. We find that optimal procedures do not involve discrete uniform distributions, because minimizing predictability is not equivalent to minimizing selection bias.

JEL classification: I1; D8; C9

Keywords: Selection bias; Clinical trials; Nash equilibrium; Restricted randomization

☆ We are grateful to John F. Stewart, Teresa Kauf and Kevin Schulman, as well as seminar participants at the National Cancer Institute Biometry Colloquium, American Statistical Association 2005 Meetings, Lehigh University Economics Workshop, and the Triangle Health Economics Workshop for helpful comments.
* Corresponding author. Tel.: +1 540 568 3180; fax: +1 540 568 3010.
E-mail address: grantwc@jmu.edu (W.C. Grant).

0167-2681/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jebo.2006.07.001

1. Introduction

For certain kinds of randomized experiments, selection bias poses a serious problem. In particular, selection bias may compromise any randomized experiment where (1) the enrollment of subjects is *sequential* and (2) the administration of treatments is *unmasked.* For randomized clinical trials, unmasking refers to when a clinical investigator learns which treatment has been assigned after the treatment is administered to a patient. A clinical trial is said to be sequential if one patient is assigned to a treatment, which is then administered to the patient, prior to the next patient being assigned to a treatment. When a clinical trial involves sequential enrollment and unmasked treatment assignments, then selection bias can result from an investigator's potential ability to predict which treatments will be assigned to future patients, based on observations of which treatments have already been assigned to earlier patients.

The choice of a randomization procedure is an important way for clinical trial statisticians to reduce expected bias, especially for sequential unmasked trials. How should a trial statistician randomize in order to minimize expected bias? In this paper, optimal randomization procedures are derived using non-cooperative game theory. We provide models of sequential games with imperfect information for three different kinds of sequential unmasked clinical trials, each involving exogenous restrictions on the imbalance between two treatments. Our results consist of rules for using optimal biased coins to randomize patients. Formally, the biased coins that we recommend constitute the statistician's best-response, consistent with subgame-perfect Nash equilibrium (SPNE).

In casual terms, our procedures differ from others by reducing bias from 'wait-and-see' strategies for enrolling patients with above-average likelihoods of response to the experimental treatment (i.e. high-responders). If some assignment history induces a subversive investigator always to wait for better treatment odds, then the statistician should increase the probability of assigning the experimental treatment at this point. Standard randomization procedures frequently allow investigators to pursue 'wait-and-see' strategies more frequently and profitably than is necessary. Our SPNE procedures diminish these hopes by adjusting the relative expected payoffs from 'wait-and-see' versus 'try-your-luck' strategies.

The paper is organized as follows. Section 2 contains background information and a simple example. Section 3 summarizes related literature. In Section 4, we describe the statistical model, as well as the objectives and game strategies available to both players (i.e. the clinical investigator and the trial statistician). The game models and subgame-perfect Nash equilibria are presented in Sections 5–7, with each section covering a different set of treatment imbalance constraints. The final section contains a discussion of empirical considerations, the feasibility of implementing optimal randomization, and conclusions.

2. Background information

Randomized clinical trials are considered the "gold standard" for testing clinical treatment effects (Hadorn et al., 1996). Conclusions drawn from randomized trials form the basis for actions taken by regulators, decisions made by clinicians, claims made by companies, and reimbursements made by payers. While randomized trials certainly provide scientifically useful evidence for comparing alternative clinical treatments, an important qualifier is frequently understated or even completely overlooked: nearly all clinical trials employ *restricted* randomization. An informed perspective on the value of clinical trial results requires an understanding of the details surrounding trials with restricted randomization procedures. Both among healthcare insiders and