Contemporary Clinical Trials 30 (2009) 129–132

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Short communication

An application of a modified constrained randomization process to a practice-based cluster randomized trial to improve colorectal cancer screening

Paul J. Nietert [a,*], Ruth G. Jenkins [b], Lynne S. Nemeth [c], Steven M. Ornstein [b]

[a] Department of Biostatistics, Bioinformatics, and Epidemiology, Medical University of South Carolina, 135 Cannon Street, Suite 303, PO Box 250835, Charleston, SC 29425, United States
[b] Department of Family Medicine, Medical University of South Carolina, Charleston, SC, United States
[c] College of Nursing, Medical University of South Carolina, Charleston, SC, United States

ARTICLE INFO

Article history:
Received 12 June 2008
Accepted 16 October 2008

Keywords:
Randomization techniques
Cluster randomized trials
Covariate balance
Study design
Practice based research networks
Colorectal cancer screening

ABSTRACT

Background: When designing cluster randomized trials, it is important for researchers to be familiar with strategies to achieve valid study designs given limited resources. Constrained randomization is a technique to help ensure balance on pre-specified baseline covariates.

Methods: The goal was to develop a randomization scheme that balanced 16 intervention and 16 control practices with respect to 7 factors that may influence improvement in study outcomes during a 4-year cluster randomized trial to improve colorectal cancer screening within a primary care practice-based research network. We used a novel approach that included simulating 30,000 randomization schemes, removing duplicates, identifying which schemes were sufficiently balanced, and randomly selecting one scheme for use in the trial. For a given factor, balance was considered achieved when the frequency of each factor's sub-classifications differed by no more than 1 between intervention and control groups. The population being studied includes approximately 32 primary care practices located in 19 states within the U.S. that care for approximately 56,000 patients at least 50 years old.

Results: Of 29,782 unique simulated randomization schemes, 116 were determined to be balanced according to pre-specified criteria for all 7 baseline covariates. The final randomization scheme was randomly selected from these 116 acceptable schemes.

Conclusions: Using this technique, we were successfully able to find a randomization scheme that allocated 32 primary care practices into intervention and control groups in a way that preserved balance across 7 baseline covariates. This process may be a useful tool for ensuring covariate balance within moderately large cluster randomized trials.

1. Introduction

"Cluster" (or "group") randomized trials (CRTs), are trials that use a cluster as the unit of randomization and cluster members as the units of analysis [1]. In contrast to traditional randomized trials in which patients are randomized, CRTs are often used in circumstances when the intervention is administered at the level of the cluster.

The use of CRTs has been steadily increasing since 1980 [2]. Within primary care research, these study designs might be becoming more popular for several reasons [3], including a greater national emphasis on improving quality of care (often requiring systems-level interventions) [4], the development and growth of practice based research networks (which often provide excellent infrastructure for CRTs) [5], and the continued adoption of electronic health records (which

* Corresponding author. Tel.: +1 843 876 1204; fax: +1 843 876 1126.
E-mail address: nieterpj@musc.edu (P.J. Nietert).

1551-7144/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.cct.2008.10.002

greatly facilitate data collection) [6]. As CRTs become more common, it is important that researchers become more familiar with the ways in which they differ from traditional randomized clinical trials.

Because CRTs often include a small number of groups relative to the number of subjects, the chance of treatment groups being imbalanced on important relevant covariates may be unacceptably high [7–9]. Should the clusters be randomized in an imbalanced fashion, it may be difficult to determine whether the estimated treatment effect is influenced by baseline imbalance. While it may be possible to control for such imbalance in the analysis phase, results may still be deemed "suspect" [10].

Several mechanisms have already been proposed for balancing baseline covariates across treatment groups. The processes, collectively referred to as "constrained randomization", have been discussed in the statistical literature since the 1970s [11,12]. These methods include stratifying clusters prior to randomization [13,14] or pairwise matching of clusters [15,16]. Such techniques are ideal when there are sufficient numbers of subjects for each stratum. However, having large numbers of strata in studies with small numbers of randomization units can be impractical because of sparseness of subjects within each stratum [12]. Additionally, imbalance may be minimized by selecting an appropriately balanced randomization scheme from all possible allocations of clusters to treatments [17,18]. However, as the number of clusters to be randomized increases, the number of possible randomization schemes grows extremely fast, and enumerating all possible randomization schemes may be impractical due to computational limitations. In this paper we propose an alternative method to achieve balance across several (>2) covariates in a CRT.

The research context is a 4-year CRT, called Colorectal Cancer (CRC) Screening in Primary Care Practice (C-TRIP). The population being studied includes 32 primary care practices located in 19 states within the U.S. that care for approximately 56,000 patients at least 50 years old. They share a common electronic medical record system and participate in a practice based research network called Practice Partner Research Network (PPRNet).

The study protocol required 16 practices to be randomized to receive a specific practice-focused intervention based upon the PPRNet quality improvement model [19,20] for improving CRC screening and 16 practices to be randomized to a usual care control group. The multi-faceted intervention incorporates quarterly provider feedback reports, semi-annual site visits by research investigators to help identify strategies for improvement, and annual network meetings. The primary outcome is the proportion of active patients 50 year of age or older up-to-date with any form of CRC screening.

Study investigators desired for the intervention and control groups to be balanced on 7 factors of interest that might influence the degree of improvement in CRC screening. Factors included baseline CRC screening performance (3 tertiles), presence/absence of state mandated insurance coverage for CRC screening, past network experience with quality improvement projects (yes/no), practice specialty (internal medicine or family medicine), number of healthcare providers (3 groupings: 1 or 2, 3 or 4, 5 or more), geographic region (East, South, Midwest, West), and whether or not the practice is a residency training program.

2. Methods

Because there were over 600 million ways to randomize these 32 practices into 2 groups, enumerating all possible randomization schemes and assessing their level of covariate balance was computationally impractical. We modified this approach by significantly reducing the number of randomization schemes being assessed. This process included simulating randomization schemes (i.e. randomly assigning the 32 practices into 1 of the 2 treatment groups, 16 practices per group), removing duplicate schemes, identifying which ones were sufficiently marginally balanced on the pre-specified covariates of interest (defined below), and randomly selecting one scheme from all possible balanced schemes, with each having an equal probability of being selected.

Table 1
Baseline comparison of practice characteristics among control and intervention practices

	Control practices (n=16)	Intervention practices (n=16)
Factors used in balancing criteria		
Geographic region		
East: *n* (%)	4 (25.0%)	3 (18.8%)
South: *n* (%)	2 (12.5%)	3 (18.8%)
Midwest: n (%)	5 (31.3%)	5 (31.3%)
West: *n* (%)	5 (31.3%)	5 (31.3%)
State-mandated CRC screening coverage		
No: *n* (%)	12 (75.0%)	12 (75.0%)
Yes: *n* (%)	4 (25.0%)	4 (25.0%)
Baseline CRC performance tertile		
Low: *n* (%)	5 (31.3%)	6 (37.5%)
Middle: *n* (%)	5 (31.3%)	5 (31.3%)
High: *n* (%)	6 (37.5%)	5 (31.3%)
Past network experience		
No: *n* (%)	12 (75.0%)	12 (75.0%)
Yes: *n* (%)	4 (25.0%)	4 (25.0%)
Specialty		
Internal medicine: *n* (%)	3 (18.8%)	2 (12.5%)
Family medicine: *n* (%)	13 (81.3%)	14 (87.5%)
Number of providers		
1 or 2: *n* (%)	6 (37.5%)	5 (31.3%)
3 or 4: *n* (%)	5 (31.3%)	5 (31.3%)
5 or more: *n* (%)	5 (31.3%)	6 (37.5%)
Residency program		
No: *n* (%)	15 (93.8%)	15 (93.8%)
Yes: *n* (%)	1 (6.3%)	1 (6.3%)
Other factors		
Number of patients 50 years and older per practice		
Median (interquartile range)	982 (743–2460)	1260 (752–2388)
Percent of patients 50 years and older up-to-date with CRC screening		
Median (interquartile range)	51.6% (44.6%–56.0%)	50.8% (44.8%–57.4%)
Average age of patients 50 years and older in each practice		
Median (interquartile range)	64.5 (62.7–67.2)	64.8 (63.6–67.0)
Percent of patients 50 years and older who are male		
Median (interquartile range)	43.0% (38.9% to 47.3%)	40.9% (38.9% to 49.1%)