A Priori Matching in Cluster Randomized Trials

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Introduction

To determine the efficacy of a treatment, individually randomized trials (IRTs) with blinding are the "strongest study design available" (**?**). Unfortunately, cost and study design amongst other things mean some interventions can not be randomized on an individual level. For example, education researchers decide to determine if training elementary school teachers in a reading program will affect literacy skills in third graders. Randomizing each third grader to treatment or control would not be suitable, as this equates to randomly allocating students to a teacher; rural schools tend to be smaller with only one teacher which further complicates matters. Instead, researchers may choose to randomize teachers, schools, or counties to determine any differences between the two arms of the study. Trials where groups are randomized are called cluster randomized trials (CRTs). Three reasons for conducting a CRTs are: (i) implementation occurs at the cluster level, (ii) to avoid contamination, and (iii) to measure intervention effects among cluster members who do not receive treatment (**??**). CRTs are "the gold standard when allocation of identifiable groups is necessary" (**?**).

Many authors debate matching in CRTs (**??????????**). Murray argues that "the choice of matching or stratification [of] factors is critical to the success of the procedure" (**?**). Some agree that caution must be used when matching a small number of clusters due to the decrease in power (**????**). Breaking matches in the analysis stage addresses this (**?**), but perhaps only when there are a small number of large clusters (**?**). Others argue that matching is effective in a small number of clusters as it "increases the chance of the intervention groups being well-balanced" (**?**). Imai et al argue that not matching, in small or large sample, is "equivalent to discarding a considerable fraction of one's data" (**?**). However, in one trial "matching actually led to a loss in statistical efficiency" (**?**, **?**).

Despite all this debate few authors discuss methodologies to support the matching process (**?**). An alternative to matching suggests balancing criterion based on conditioned means of covariates (**?**). ZUBIZARRETA (**?**). Our article is an extension of methods introduced in Chapter 4 of Methods in Comparative Effectiveness Research (**?**). We suggest a method suitable for *a priori* matching using baseline data. In section 2 we outline our method, section 3 applies it to the SWAPOUT dataset, and section 4 is a brief discussion.

Methods

To approach this complex topic of balancing randomization in CRTs we suggest a new approach. Our approach involves weighting variables of import, matching units using these weights, and randomizing many times to obtain a distribution of possibilities when official randomization occurs. Investigators assess these distributions to determine if possible randomizations are sufficiently balanced, if not, weighting is adjusted and the process begins again. The details follow.

The initial step involves prioritizing variables $(1, 2, ..., m)$ from units $(1, 2, ..., n)$ to be randomized. We have

$$\begin{aligned}
\overline{V_1} &= (v_{11}, v_{12}, ..., v_{1n}) \\
\overline{V_2} &= (v_{21}, v_{22}, ..., v_{2n}) \\
\vdots &= \vdots \\
\overline{V_m} &= (v_{m1}, v_{m2}, ..., v_{mn}).
\end{aligned}$$

In addition, we use $\overline{w} = (w_1, w_2, ..., w_m)$ to weight and standardize $(\overline{V_1}, \overline{V_2}, ..., \overline{V_m})$. We have

$$v_{ij}^* = \frac{(v_{ij} - \frac{\sum_{k=1}^{n} v_{ik}}{n}) * w_i}{sd(\overline{V_i})}$$

where $sd(\overline{V_i})$ is the standard deviation of $\overline{V_i}$. We now have

$$\begin{aligned} \overline{V_1^*} &= (v_{11}^*, v_{12}^*, ..., v_{1n}^*) \\ \overline{V_2^*} &= (v_{21}^*, v_{22}^*, ..., v_{2n}^*) \\ \vdots &= \vdots \\ \overline{V_m^*} &= (v_{m1}^*, v_{m2}^*, ..., v_{mn}^*). \end{aligned}$$

which we use to compute the Mahalanobois Distance matrix, $\mathbf{D}$. From here we use the `nmatch` function in the `designmatch` (**?**) package in `R` (**?**)to find $\frac{n}{2}$ pairs if n is even. If n is odd, the remainder can be randomized to treatment or control per the principal investigator. Without loss of generality, we assume n is even for the remainder of this paper and note that to include an odd n either treatment or control groups will include one more set of priority variables.

Once the matching is completed and pairs found we return to using the raw data, as this will be used to assess the weighting scheme. We now have pairs $(\overline{V}_{11}, \overline{V}_{12}), (\overline{V}_{21}, \overline{V}_{22}), ..., (\overline{V}_{\frac{n}{2}1}, \overline{V}_{\frac{n}{2}2})$. The first match in each pair will be randomized to either treatment or control using the `rbinom` function in `R`. Next, we subset $\overline{V}_1, \overline{V}_2, ..., \overline{V}_m$ into appropriate randomization subgroups: $\overline{V}_{1T}, \overline{V}_{1C}, \overline{V}_{2T}, \overline{V}_{2C}, ..., \overline{V}_{\frac{n}{2}T}, \overline{V}_{\frac{n}{2}C}$ where $\overline{V}_{iT} = (v_{i1}^T, v_{i2}^T, ..., v_{in}^T)$, similarly for $\overline{V}_{iC}$. Using these we find

$$k_j = |\sum_{i=1}^{\frac{n}{2}} v_{ij}^T - \sum_{i=1}^{\frac{n}{2}} v_{ij}^C|$$

THE ABOVE NEEDS A BETTER ABSOLUTE VALUE SYMBOL. for $j = 1, 2, ..., m$. We randomize N times and find k_{lj} the difference in the two arms for the j^{th} priority variable for each of the $l = 1, 2, ..., N$ re-randomizations. To assist analysis we draw a parallel coordinates plot where the j^{th} axis plots k_{lj} for $l = 1, 2, ..., N$. If the principal investigator finds the possible differences too large for a priority variable j, increasing w_j and re-running the above will update the matching to attain closer matches for this variable and lessen the differences. The penality in this process is that closer matches for variable j are likely to imply reduced closeness in another variable, so compromises must be made.

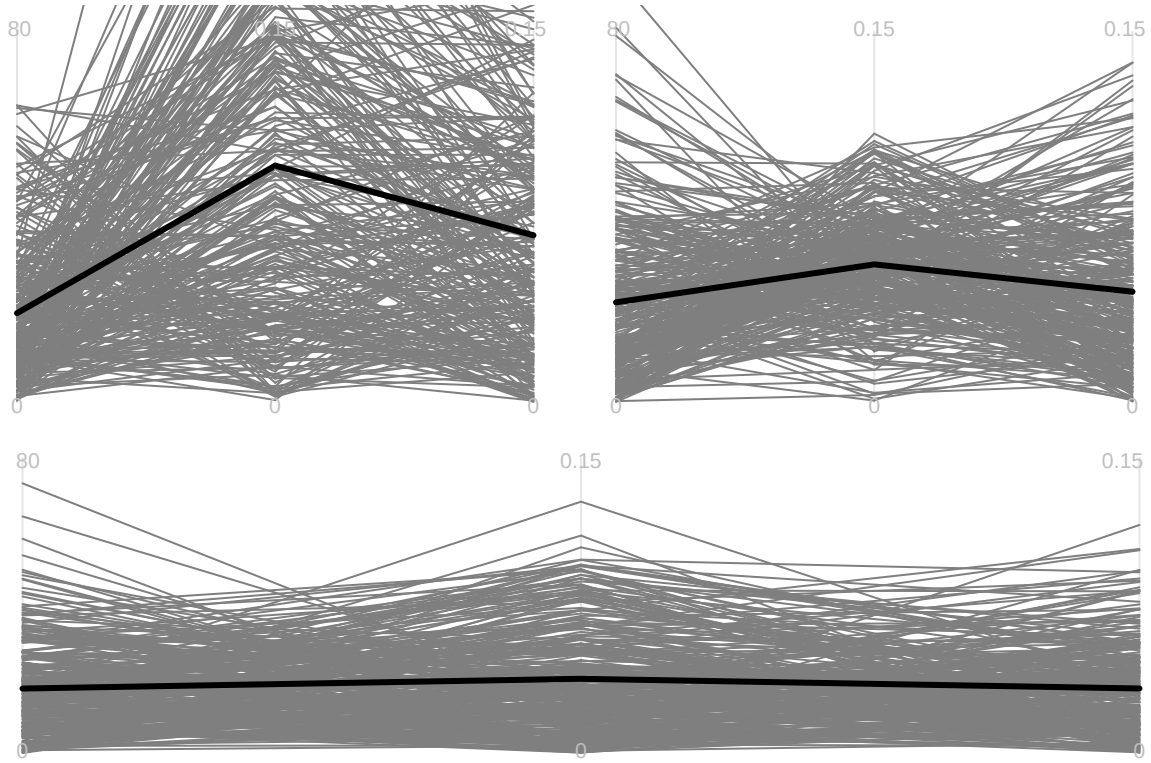
Results

To demonstrate the usefulness of this technique we present a brief summary of our randomization process using baseline data from the SWAPOUT trial (Cluster-randomized Non-inferiority Trial Comparing Mupirocin vs Iodophor for Nasal Decolonization of ICU Patients to Assess Impact on Staphylococcus aureus Clinical Cultures and All-cause Bloodstream Infection During Routine Chlorhexidine Bathing) (**?**). In this non-inferiority trial, the investigators are studying whether bathing with chlorhexidine gluconate and swabbing iodophor nasal swabs are inferior to bathing with the same and mupirocin nasal swabs. REDUCE trial ADD REF mupirocin nasal swabs and bathing with chlorhexidine reduced the MRSA Staphylococcus aureus (an antibiotic resistant infection) in Hospital Corporation of America intensive care units (ICU). However, physicians are reluctant to use mupirocin, an antibiotic, so investigators are swapping it with iodophor.

Prior to randomization baseline data was collected for 20 months on the 137 hospitals. With this data, investigators met to prioritize baseline variables into several categories: primary, secondary, tertiary, quaternary, and not relevant to randomization. For this trial, the investigators decided that average monthly volume of patients with attributable time, average monthly attributable days, Staphylococcus aureus ICU-attributable cultures per 1,000 days, MRSA ICU-attributable cultures per 1,000 days, all pathogen ICU-attributable bacteremia cultures per 1,000 days, regional mupirocin resistance estimate, percent of admissions with MRSA diagnosis within a year, percent of mupirocin use admission to day 5, survey Chlorhexidine Glucominate were all of primary importance. Of secondary importance were median ICU length of stay, and mean elixhauser total score. Of tertiary importance were the percentage of ICU medicaid patients, and Polymerase chain reaction clinical specimen status. Lastly, percent admissions to skilled nursing facility (SNF), and if the ICU has specialty units for burn, trauma, etc. A list of abbreviations in the above order can be found in Table 1. To ease understanding, our initial discussion will involve 3 variables: Patient days, Staphylococcus auer rate, and MRSA rate.

Table 1. Abbreviations of variables used to randomize

Primary import	Secondary import	Tetiary import	Quaternary import
Pt Days	Median LOS	Medicaid	
S auer Rate	Comorbidity Score	TALI WHAT ELSE??	
MRSA Rate			
All Blood			
Mup-R			
Hx MRSA			
Mup Adherence			
CHG Adherence			



Prior to randomization, investigators spent time using a web application built using the `Shiny` package in `R`. The purpose of this is to determine which weights give advantageous balance across relevant baseline variables.

Discussion

Look how smart we are.

Appendix

A more formal explanation of the variables here, to be checked with Susan.

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