MinimRan: A robust online system to implement minimization in randomized clinical trials

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Abstract

Despite its theoretically and empirically supported appeal for being able to achieve balance allocation across multiple prognostic factors, minimization remains uncommonly used in clinical trials owing to a lack of implementation tools. To fill this gap, we have developed a robust, flexible, and readily accessible Web-based treatment allocation system, MinimRan (http://studies.pamfri.org:8080/minimRan/index.jsp), in order to promote broad adoption of minimization into clinical research practice. The system currently provides the Pocock–Simon, two-way, and symmetric Kullback–Leibler divergence (KLD) minimization methods. It can support single- and double-blind trials as well as single-center and multicenter trials. MinimRan's ability to ensure double-blinding through a sophisticated, nevertheless user-friendly, role management capability distinguishes it from other existing minimization websites. MinimRan also has robust data management and report functions that enable researchers continuously monitor the randomization process, detect, prevent and correct errors, and verify randomization results. This paper will showcase MinimRan's core functionalities and discuss future development.

Key Words: Minimization, Covariate adaptive randomization, Web-based randomization

1. Background

Randomized controlled trials (RCTs) are the gold standard for assessing efficacy or effectiveness of biomedical and behavioral treatments. The validity of a randomization method should be judged on the absence of accidental and selection bias and balanced arm sizes. However, no randomization procedure can perfectly meets all of these criteria in every circumstance. Simple randomization minimizes selection bias but cannot reliably prevent unequal arm sizes or accidental bias[1]. Minimization, on the other hand, controls accidental bias and unequal sample sizes across treatment groups, but strict minimization[2,3] is deterministic based on the information of the previously assigned subjects combined with the levels of covariates of the next assigning subject[4]. Any method to improve the prospects for balance makes a tradeoff in randomness. The Pocock-Simon minimization[5], widely known as the covariate-adaptive biased coin randomization procedure, incorporates probability in favor of minimizing overall

imbalance across covariates. The common choice of a 2/3 allocation probability is justified by a favorable comparison of the biased coin to blocked randomization in terms of achieving the same unpredictability as a block size of 16-18[6]. The two-way minimization method protects unpredictability by probabilistically minimizing the imbalance either in the total numbers of subjects or the distribution of prognostic factors[7]. Both the Pocock-Simon and two-way minimization methods only allow for categorical balancing factors. However, categorizing continuous covariates may not always be feasible or preferable (e.g., owing to a lack of scientific basis for or consensus on cut points). Endo et al.[8] extended the Pocock-Simon approach to incorporate continuous prognostic factors in two-arm trials using the symmetric Kullback-Leibler divergence (KLD) (i.e., Jeffrey's divergence) index[9, 10]. Despite their notable advantages and recommended use by many methodologists and clinical trialists[11], these minimization methods remain infrequently used, to a large extent because easily accessible tools are lacking[12].

To promote increasing use of minimization methods in various study designs and settings, we developed a robust web-based randomization system named, "MinimRan," with flexible and user-friendly features. A full description of MinimRan's statistical and computer programming details can be found elsewhere[13]. The purpose of this conference proceeding paper is to highlight the system's core functionalities, provide an example of its implementation, and discuss plans for future development.

2. Methods

2.1 System Design

MinimRan uses a three-tier architecture (presentation tier, logic tier, and data tier), the most widely used browser-server architecture, to support the web-based random allocation system (http://studies.pamfri.org:8080/MinimRan/index.jsp). The system provides sequential covariate-balanced assignment of subjects in single- or double-blind and single- or multi-center trials by using convenient graphical user interfaces (GUI) for information input and output through a web browser.

2.2 Choice of Minimization Method

All three minimization methods (Pocock–Simon[5], two-way[7], and symmetric KLD[8]) the system currently offers can simultaneously minimize the overall imbalance and maintain allocation concealment. Users may choose any of the three methods based on the trial design, the number of treatment arms, and the type of prognostic factors. Both the Pocock-Simon and two-way minimization methods require continuous prognostic factors be categorized to calculate overall imbalance score. The algorithm for the Pocock-Simon minimization method is the marginal treatment totals across all levels of all balancing factors[14], whereas the two-way minimization method computes one imbalance score for the total number of subjects and the other for the distribution of prognostic factors. Endo et al.'s symmetric KLD index measures the overall imbalance across covariates, which may be continuous and/or categorical. At present, only Pocock-Simon's method can be used in trials with more than two arms.

2.3 User-project Role Management

Three types of users—Super, Project Manager, and General—can access the system with different privilege settings. The Super user functions as system administrator, a role retained by the system developer. Upon obtaining authorization by Super user, the Project

Manage user can create new projects and General User accounts with individual specific privileges. Depending on the assigned privileges, the General User may perform randomization, access individual group assignment, monitor randomization, manage randomization results, and update project information. The Third Party user is a special General User type in double-blind trials, whose only privilege is to access masked individual numbers with the matching coded group assignment numbers. Each user account can have different access privileges for different projects.

2.4 Protections of blinding

In single-blind trials, users not assigned the privilege of 'Access individual group assignment' is automatically blinded to the randomization results.

In double-blind trials, the system generates a Masked_Num table upon Project Manager completing the project initiation steps and before randomization of the first subject. The table contains masked numbers and matching coded group numbers or names (by study site if a multi-site trial), which only a designated Third-Party General User can access and download (as a CSV file) for encoding the treatments (e.g., using masked numbers on drug bottle labels for distribution and tracking). The system provides Project Managers and General Users performing randomization in double-blind trials with subjects' assigned masked numbers but not the associated group numbers.

2.5 Randomization process monitoring

Project Managers has the ability to view and verify randomized records as appropriate to their blinding status (e.g., only masked numbers if a double-blind trial) on a given project. The system also provides standardized summary reports for continuous, timely quality monitoring of the randomization process. The detailed randomization process data are retrievable to permit quality control and replication. A Project Manager with permission to access group assignments can download randomization process data for his/her current and expired single-blind trials. For double-blind trials, however, the data can be requested from the Super User only if the Project Manager attests in writing that the trial has broken the blind.

2.6 Information updates and error corrections

Throughout the randomization process in a trial, the system gives users the option of uploading records with subject IDs and prognostic factors for randomization as a CSV data file or manually entering records one at a time. To ensure data validation, the system prompts the user to verify the inputted subject information, and checks for errors using the logic rules defined by the Project Manage during study setup and generates alerts if any rule is violated before the user can proceed with randomization.

Any data errors detected after randomization may only be corrected by the Project Manager, who also must specify the reason. The existing randomization results before the correction will remain unchanged, although randomization of any new subjects will be based on the corrected information. The action of revision will be recorded and traceable in the randomization process data for trial monitoring and audits.

The allocation probabilities defined during project initiation can be adjusted by the Project Manager after randomization has begun, if warranted (e.g., if the initial probabilities lead to imbalance scores exceeding the pre-specified threshold in a given study).

3. Results

To date, we have implemented MinimRan in several of our RCTs. The most recently completed study is a clinical trial pilot study of the Dietary Approaches to Stop Hypertension (DASH) in adults with uncontrolled asthma (ClinicalTrials.gov identifier NCT01725945). The trial protocol was previously published.[15] Below we summarize the randomization process and balancing results of MinimRan in this trial as an example of actual implementation.

3.1 Project set-up

Project Manager defined the project "DASH" after the Super User had created and assigned the project to her account, where DASH was shown as "Pending" in "Current Projects." and The project status changed to "Ongoing" once the following study parameters were defined :
Single- or double-blind trial: Single-blind; number of study groups: 2; minimization method selected: Pocock-Simon; biased assignment probability: 2/3 and 1/3; prognostic factors, and levels of each categorical factor: 7-item Juniper asthma control questionnaire score ACQ_score (1(<1.5) and 2 (>=1.5)), age (1 (18-<45), 2 (45-<60), 3 (60+)), Dash concordance index DASH_score (1 (0-1), 2 (1.5-2.5), 3 (3+)), race (1 (Hispanic), 2 (Non-Hispanic White), 3 (Non-Hispanic Black), 4 (Asian/Pacific Islander), 5 (Other)), sex (0 (Male), 1 (Female)), study site SITE1(HP (Hayward), SP (San Francisco)), smoking status (0 (Never Smoker), 1 (Current Smoker), 2 (Former Smoker)).

It is important that prognostic factors are clearly defined and documented in the study protocol. MinimRan does not permit addition or modification of the prognostic factors after the project setup is finalized.

Project Manager also created several General User accounts with different access privileges. DASH was a single-blind trial; outcome assessors were blinded and thus not assigned the privilege of "Access individual group assignment," but by design the interventionists were unblinded.

3.2 Allocation and process monitoring

We started with 2852 potentially eligible patients identified from the asthma registry of the participating clinics, and 1019 of them were approved by primary care providers for study contact and screening. Ninety participants proved fully eligible based on study entry criteria after completing initial screening, group orientation, and baseline visit.

The 90 study participants were sequentially enrolled and randomized. Participant data for the balancing prognostic factors were extracted and combined into a CSV file, which an interventionist could upload into MinimRan for randomization. The Project Manager monitored the balance of group sizes and prognostic factors by periodically reviewing the updated standardized reports, "Summary for first n subjects," in MinimRan.

3.3 Randomization results

The summary table (below) of the 90 randomized participants, which was generated by MinimRan (with the exception of the *P* values), shows better than chance balance between the two treatment arms across all seven prognostic factors.

Table. Between-group differences in prognostic factors for the DASH study

Factor	Level	Numbers by group		Total	Max Group Difference	P value
		Group 1 (1)	Group 2 (2)			
ACQ_SCORE	1	31	26	57	5	0.50
	2	15	18	33	3	
AGE	1	13	13	26	0	
	2	21	17	38	4	0.77
	3	12	14	26	2	
DASH_SCORE	1	9	12	21	3	
	2	19	17	36	2	0.43
	3	18	15	33	3	
RACE	1	6	7	13	1	
	2	21	18	39	3	
	3	6	4	10	2	0.85
	4	13	15	28	2	
	5	0	0	0	0	
SEX	0	13	17	30	4	
	1	33	27	60	6	
SITE1	HP	25	26	51	1	0.65
	SP	21	18	39	3	
SMOKING_STATUS	0	37	30	67	7	
	1	2	3	5	1	0.48
	2	7	11	18	4	
Total		46	44	90	2	

4. Conclusions

MinimRan is a web-based randomization system designed to facilitate the use of the Pocock-Simon, symmetric KLD, and two-way minimization methods in RCTs. It provides user-friendly and error-resistant web interfaces that are applicable to single- and double-blind trials in single- and multi-center settings.

Our experiences in several trials (including DASH) show that a 2/3 allocation probability provides good overall balance in terms of prognostic factors and arm sizes and simultaneously protects unpredictability. Through continuous monitoring of balancing measures, we have also found that probability= (2/3, 1/6, 1/6) for 3-arm RCTs and probability= (2/3, 1/3) for 2-arm RCTs produce stable performance over the course of enrollment even in small trials, such as DASH.

MinimRan provides a comprehensive error checking and correction mechanism before and after randomization. However, as noted, if error is not detected until after randomization of the erroneous record has occurred, the randomization outcomes up to that point shall remain unchanged even though subsequent records will be randomized based on corrected prior data. This only reinforces the essentiality of continuous data quality management and verification.

5. Future work

The purpose of developing MinimRan is to facilitate translation of validated randomization methods into broad, efficient use in clinical research. Since our original publication[13], we have received numerous requests for access to the system from statisticians and clinician researchers in academia and industry in the US and abroad. We are in the need of seeking external funding to support such expanded services. In addition to the existing features as summarized above (see further details in our prior publication), our team can tailor the system to users' specific needs. For example, MinimRan can be customized for integration with electronic data capture (EDC) or clinical trial management (CTM) in industry trial settings and electronic health record (EHR) systems in academic and private or public healthcare systems. We also plan to include more randomization methods, such as dynamic block randomization[16], which has been developed in the R software.

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