

randomizeR: An R Package for the Assessment and Implementation of Randomization in Clinical Trials

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Abstract

This introduction to the R package **randomizeR** is a slightly modified version of [Uschner, Schindler, Hilgers, and Heussen \(2018\)](#).

Randomization in clinical trials is the key design technique to ensure the comparability of treatment groups. Although there exist a large number of software products which assist the researcher to implement randomization, no tool which covers a wide range of procedures and allows the comparative evaluation of the procedures under practical restrictions has been proposed in the literature.

The R package **randomizeR** addresses this need. The paper includes a detailed description of the **randomizeR** package that serves as a tutorial for the generation of randomization sequences and the assessment of randomization procedures.

Keywords: restricted randomization procedure, selection bias, chronological bias, R.

1. Introduction

Randomization is a design technique to ensure the comparability of treatment groups in clinical trials by introducing a deliberate element of chance. [Armitage \(1982\)](#) states the three main goals that are supposed to be achieved by randomization. First, it tends to balance known and unknown covariates and, thus, to produce structural equality of the treatment groups. Second, by ensuring effective blinding of treatment allocations from investigators and patients, randomization helps to avoid bias caused by the selection of patients. Finally, randomization contributes to the internal validity of a trial that provides the basis for statistical inference. The importance of randomization for clinical trials was first noted in the 1940s by Sir A. Bradford Hill (see [Chalmers 1999](#)) who realized that successful blinding of treatment allocations was impossible without randomization. Since that time, regulators have advocated the use of randomization in their guidelines (see for example [ICH E9 1998](#)) and several different randomization procedures have been proposed in the literature. It has been noticed that different randomization procedures behave differently, e.g., concerning their susceptibility to bias and their potential to control power and type-I-error probability. An overview containing the latest developments can be found in [Rosenberger and Lachin \(2016\)](#).

Despite the importance of randomization in the context of clinical trials, the novelties of the

last decades have hardly found their way into clinical practice. Berger, Bejleri, and Agnor (2015) remark that clinicians stick with randomization procedures that are easily available, although their poor properties have been widely discussed and better alternatives have been proposed. Notably, the most suitable randomization procedure may depend on the clinical context. For example, when block randomization is used, Tamm and Hilgers (2014) advocate small block sizes to control chronological bias, while Kennes, Hilgers, and Heussen (2012) show that larger blocks are better to control selection bias.

The choice of an adequate randomization procedure is crucial to achieve favorable properties such as control of power and type-I-error rate, especially for small sample sizes where asymptotic assumptions do not hold. However, no software package exists that assists the user in choosing a randomization procedure based on scientifically sound criteria, as we revealed in a literature review (see Appendix A). The R package **randomizeR** addresses this need. It combines the assessment of randomization procedures on the basis of scientifically sound criteria with the generation of randomization lists for clinical trials, creation of randomization protocols, extensive documentation and open source license. In addition, it contains fourteen randomization procedures. Existing software tools such as the **blockrand** package by Snow (2013) implement only a very limited number of randomization procedures. The special class of response-adaptive randomization procedures is not included in **randomizeR**, but has currently been implemented for trials with time-to-event outcome in the MATLAB package **RARtool** by Ryznik, Sverdlov, and Wong (2015).

This article gives a detailed description of the **randomizeR** package. It is organized as follows. Section 2 presents the background for assessing the properties of randomization procedures such as susceptibility to bias with references to existing literature. Particularly, the randomization procedures are presented in Section 2.3. Section 3 shows how **randomizeR** implements the methods from the background chapter. Particularly, Section 3.2.2 provides a tutorial for the generation of randomization lists with **randomizeR**, and Section 3.3.1 illustrates the assessment of randomization procedures with respect to the different types of bias and other criteria.

2. Assessing the properties of randomization procedures

2.1. Notation and model

We consider the case of a two armed clinical trial with parallel group design and total sample size N . Let A and B be treatments that influence a continuous outcome Y . A *randomization procedure* \mathcal{M} is a probability distribution on the space $\Omega = \{0, 1\}^N$. A *randomization sequence* is an element $t \in \Omega$, where $t_i = 1$ if patient i is allocated to treatment A and $t_i = 0$ otherwise. Let $T = (T_1, \dots, T_N)$ denote a random variable with probability distribution \mathcal{M} taking values in Ω . Throughout the paper, let the outcome y_i of patient $i = 1, \dots, N$ be the realization of a normally distributed random variable

$$Y_i \sim \mathcal{N}(\mu_A \cdot T_i + \mu_B \cdot (1 - T_i), \sigma^2) \quad (1)$$

with group expectations μ_A, μ_B and equal but unknown variance $\sigma^2 > 0$. The outcome y_i is called *response*. Higher values of the response are regarded as better. We test the null hypothesis that the expectation of the experimental treatment A does not differ from the

expectation of the control treatment B against the two-sided alternative

$$H_0 : \mu_A = \mu_B \quad \text{vs.} \quad H_1 : \mu_A \neq \mu_B. \quad (2)$$

When the response Y_i of patient i is influenced by an unobserved quantity b_i , we call b_i *bias* of the i -th patient. Bias includes selection bias or chronological bias, or both, as proposed in the Section 2.2.1 and Section 2.2.2. We investigate how the randomization procedures manage the misspecification of the model

$$Y_i \sim \mathcal{N}(\mu_A \cdot T_i + \mu_B \cdot (1 - T_i) + b_i, \sigma^2) \quad (3)$$

with b_i the fixed bias of patient i .

2.2. Criteria for the assessment

The potential of a randomization procedure to control the impact of bias on the study results along with other exemplary criteria for the choice of a randomization procedure are summarized in this section. The assessment of the impact of bias is important if the form of the bias is unknown or the bias is unobserved.

Susceptibility to chronological bias

Changes in study environment, e.g., increased diagnostic potential, may impact the response to treatment over time. Unobserved time trends lead to a bias of the estimator of the treatment effect, for which [Matts and McHugh \(1978\)](#) used the term *chronological bias*. Chronological bias is a special case of accidental bias as introduced by [Efron \(1971\)](#). Efron investigated the effects of covariates that have been (unintentionally) ignored in the model. Although the underlying trend could in theory be included in the model, the bias is often unobserved, or the exact form is unknown. Furthermore, especially in small population groups, it is challenging to use models with many explanatory variables. [Rosenkranz \(2011\)](#) measured the impact of chronological bias by the distortion of the type-I-error rate of the t test when the responses are influenced by a trend $\tau(i, \vartheta)$:

$$Y_i \sim \mathcal{N}(\mu_A \cdot T_i + \mu_B \cdot (1 - T_i) + \tau(i, \vartheta), \sigma^2). \quad (4)$$

The parameter ϑ denotes the strength of the time trend. [Tamm and Hilgers \(2014\)](#) proposed three shapes of trend that are summarized in Table 1. For the step trend, they introduce an index $1 \leq n_0 \leq N$ where the trend function $\tau(i, \vartheta)$ jumps from zero to ϑ . Hence, the function $1_{\{i \geq n_0\}}$ yields the value one if $i \geq n_0$ and zero if $i < n_0$. The function \log denotes the natural logarithm.

Susceptibility to selection bias

Sir A. Bradford Hill was the first to adopt randomization in clinical trials (see [Chalmers 1999](#)). His aim was to ensure effective blinding and to avoid bias due to the conscious or unconscious selection of patients to treatment groups, the so-called *selection bias*. We consider two measures for selection bias proposed in the literature, the expected number of correct guesses and the influence of selection bias on the test decision.

Trend	Shape
Linear	$\tau(i, \vartheta) = i \cdot \vartheta$
Logarithmic	$\tau(i, \vartheta) = \log(\frac{i}{N}) \cdot \vartheta$
Step	$\tau(i, \vartheta) = 1_{\{i \geq n_0\}} \cdot \vartheta, n_0 \in \{1, \dots, N\}$

Table 1: The three types of time trend included in **randomizeR**.

The expected number of correct guesses was introduced by [Blackwell and Hodges \(1957\)](#). They assume that, based on past treatment assignments, the investigator consciously or unconsciously guesses the next treatment based on the past assignments. Suppose the investigator guesses that patient $i > 1$ will receive treatment $g(t, i) \in \{A, B\}$ based on the previous assignments (t_1, \dots, t_{i-1}) . The correct guesses of a randomization sequence is the number of assignments the investigator guesses correctly:

$$CG(t) = |\{i \in \{1, \dots, N\} : g(t, i) = t_i\}|. \quad (5)$$

Two guessing strategies were investigated by [Blackwell and Hodges \(1957\)](#). Under the *convergence strategy (CS)*, the investigator assumes that the next patient is assigned to the group that has so far been assigned less. Under the *divergence strategy (DS)* the experimenter assumes that the next patient is assigned to the treatment that has so far been observed more often. At the beginning of the trial and when there is a tie, the investigator guesses the next allocation at random.

The expected number of correct guesses $E(CG(t))$ reflects the predictability of a sequence $t \in \Omega$. The overall predictability of a randomization procedure \mathcal{M} is given by the average proportion of correct guesses:

$$avpCG_{\mathcal{M}} := \frac{1}{N} \cdot E_{\mathcal{M}}(E(CG(t))).$$

[Proschan \(1994\)](#) proposed to measure the influence of selection bias on the test decision when the responses are biased as a result of selecting the patients following the convergence strategy:

$$Y_i \sim \mathcal{N}(\mu_A \cdot T_i + \mu_B \cdot (1 - T_i) - \text{sign}(D_i) \cdot \eta, \sigma^2), \quad (6)$$

where $D_i := D_i(T) = \sum_{j=1}^i T_j - \sum_{j=1}^i (1 - T_j)$ denotes the *imbalance* of a randomization sequence, $\text{sign}(x)$ denotes the sign function, and η denotes the selection effect. [Tamm, Cramer, Kennes, and Heussen \(2012\)](#) demonstrated the impact of selection bias for different values of the selection effect η .

Balancing behavior

According to [ICH E9 \(1998\)](#), it is desirable for a randomization procedure to balance the group sizes throughout the trial as well as at the end of the trial, while avoiding predictability. [Table 2](#) summarizes the measures for the imbalance that have been proposed in the literature (see for example [Atkinson 2014](#)). According to [Lachin \(1988\)](#) imbalance may cause decreased power of the statistical test in case of continuous endpoint and homoscedasticity.

Imbalance	Formula
Final	D_N
Absolute final	$ D_N $
Maximal	$\max_{i=1,\dots,N} D_i $
Loss	$\frac{D_N^2}{N}$

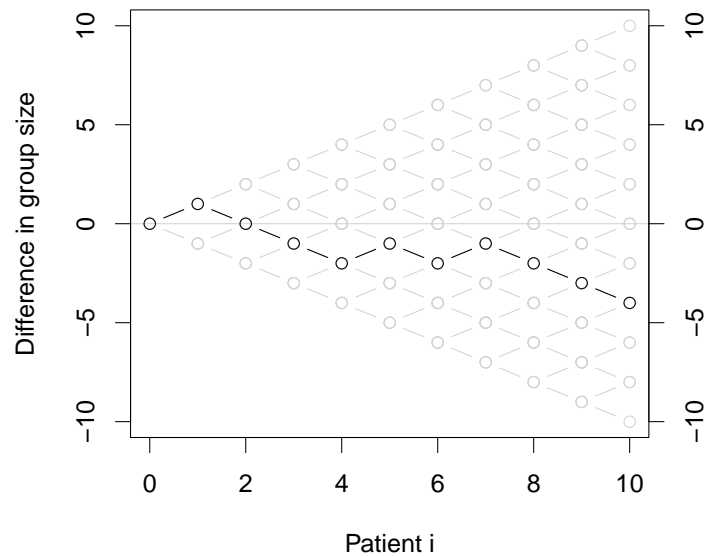
Table 2: Imbalance measures implemented in **randomizeR**.

Figure 1: Random walk of the randomization sequences of CR.

2.3. Randomization procedures

Randomization procedures can be described in terms of a restricted or unrestricted random walk (see [Proschan 1994](#)). The restrictions imposed on the random walk lead to different randomization procedures. In this section, we give a short overview about the randomization procedures that are implemented in **randomizeR**. For a comprehensive overview we refer to [Rosenberger and Lachin \(2016\)](#).

Complete Randomization (CR) is equivalent to tossing a fair coin for the allocation of each patient. CR leads to 2^N equi-probable sequences where N denotes the total sample size. Figure 1 shows a randomization sequence produced by a CR in heavy black, along with all possible sequences in light gray.

Using Random Allocation Rule (RAR), patients are allocated by drawing N times without replacement from an urn consisting of $N/2$ balls for each treatment. RAR produces $\binom{N}{N/2}$ equi-probable sequences that all attain final balance.

Permuted Block Randomization (PBR) with *block constellation* $bc = (k_1, \dots, k_m)$ balances the allocations in the blocks of length k_1, \dots, k_m . For each block $j = 1, \dots, m$, an urn is filled with $k_j/2$ balls for each of the two treatments, and k_j balls are drawn without replacement from the urn. PBR leads to $\prod_{j=1}^m \binom{k_j}{k_j/2}$ equi-probable sequences that attain balance after each block, particularly at the end.

Permuted Block Randomization with *random block constellation* (RPBR) is similar to PBR, but the block constellation bc is sampled at random from the set of given block lengths rb . RPBR permits two variations (Heussen 2004; Rosenberger and Lachin 2016): The entries k_j of bc can either be drawn uniformly with replacement from rb until $\sum k_j \geq N$, or be conditioned to achieve final balance, namely $\sum k_j = N$.

The Truncated Binomial Design (TBD) consists of tossing a fair coin for the allocation of patients until $N/2$ heads or tails have occurred. The remaining patients are allocated deterministically to the opposite group. TBD results in sequences that attain final balance but are not equiprobable. TBD admits the same number of sequences as RAR. As an extension, TBD can be conducted in blocks similar to PBR, or similar to RPBR with random block constellation (RTBD).

The Maximal Procedure (MP) was proposed by Berger, Ivanova, and Knoll (2003). MP gives equal probability to all sequences that attain final balance and do not exceed a pre-specified maximum tolerated imbalance $mti \in \mathbb{N}$. Always when the imbalance boundary is reached, i.e., $|D_i| = mti$, a deterministic assignment is made to the underrepresented group in order to reduce the imbalance.

The Big Stick Design (BSD) introduced by Soares and Wu (1983) consists of tossing a fair coin until the imbalance $|D_i|$ reaches a maximum tolerated imbalance $mti \in \mathbb{N}$.

In Efron's Biased Coin design (EBC) (see Efron 1971), a biased coin is tossed for the next allocation in order to reduce the imbalance with probability $0.5 \leq p \leq 1$. When the groups are balanced, a fair coin is tossed.

Chen (1999) proposed a biased coin design with imbalance tolerance (CHEN) that combines BSD and EBC. When the groups are balanced, a fair coin is tossed for the allocation of patients. Otherwise, a biased coin with probability $0.5 \leq p \leq 1$ is tossed until reaching an imbalance boundary $mti \in \mathbb{N}$. When the imbalance boundary is reached, a deterministic assignment is made in order to reduce the imbalance.

The Accelerated Biased Coin Design (ABCD) proposed by Antognini and Giovagnoli (2004) uses the toss of a biased coin for the allocation of patients. The probability $p_i = p(D_{i-1}, a)$ for allocating the i th patient to the experimental group depends on the imbalance D_{i-1} and an *acceleration parameter* $a > 0$. The acceleration parameter exponentially weights the imbalance and thus determines the degree of randomness of the design.

The Bayesian Biased Coin Design (BBCD) proposed under the name 'dominant biased coin design' by Antognini and Zagoraiou (2014) is similar to ABCD. Here, the probability p_i of allocating the i th patient to the experimental group depends on the acceleration parameter $a > 0$ and the ratio $N_A(i-1)/N_B(i-1)$ where $N_A(i-1)$ and $N_B(i-1)$ are the numbers of patients in groups A and B respectively after allocating $i-1$ patients.

Wei's Urn Design (UD) consists of N draws of an urn whose composition is updated after each draw. Before allocating the first patient, the urn contains an initial number ($ini \geq 0$) of balls of different colors for each treatment. For the allocation of a patient, a ball is drawn,

the color is noted, and replaced along with an additional number ($add \geq 0$) of balls of the of the opposite color.

The Generalized Biased Coin Design (GBCD) was developed by Smith (1984) to extend various designs. A biased coin is tossed for the allocation of patients, where probability of allocating the next patient to the experimental group depends on $N_A(i-1)$ and $N_B(i-1)$ as well as a balancing parameter $\rho \geq 0$.

The Hadamard Randomization (HADA) proposed by Bailey and Nelson (2003) uses the rows of a special Hadamard matrix $H \in \{0, 1\}^{11 \times 12}$ for the allocation of patients. Rows from H are sampled until the number of allocations reaches the planned sample size N .

Table 3 in the next chapter shows how the presented randomization procedures can be used in **randomizeR**.

2.4. Implementation

The assessment of a randomization procedure is based on a set of allocation sequences. Some of the assessment criteria, for example type-I-error or power, depend on a response, while others, e.g., correct guesses, are independent of a response. There are two different options to generate a set of allocation sequences depending on the sample size N , and two different methods to calculate the response based assessment criteria:

Complete or simulated reference set: In case of $N \leq 24$, it is possible to generate the set of all possible allocation sequences $\{0, 1\}^N$, assess the eligibility of an allocation sequence and, independently, calculate the associated probabilities for the allocation sequences by the randomization algorithm. This results in the *complete set* of the sequences. The function `getAllSeq` provides this functionality, see Section 3.2.3.

In case of $N > 24$, the complete set cannot be calculated in reasonable time. Instead, a number r of allocation sequences is generated undergoing the randomization algorithm of the particular randomization procedure. The function `genSeq` provides this functionality, see Section 3.2.3. Formally, the relative frequencies of the allocation sequences can be used to estimate the true probabilities of allocation sequences. Note therefore that, in a simulation, the relative frequency of a randomization sequence is used. This results in the *simulated set* of the sequences. The simulated set can also be applied in case of smaller sample sizes, and procedures where the exact approach is not available in the literature, i.e., Block Randomization with random block constellation and Hadamard Randomization.

Exact or simulated response based assessment criteria: The susceptibility of a randomization procedure to bias can be measured as the distortion of the type-I- or type-II-error probability. The *exact method* computes the distribution of the exact rejection probabilities. For each randomization sequence in the reference set, the rejection probability of Student's t test is calculated using the knowledge on the b_i from Model 3 (see Langer 2014, Chapter 4). The *simulation method* simulates a response vector for each allocation sequence in the reference set according to Model 3 and derives a test decision of Student's t test. The type-I- or type-II-error *rate* is computed as the proportion of falsely rejected test decisions. This method was used for example by Proschan (1994). Section 3.3 shows how the exact and simulated type-I- and type-II-error probabilities can be assessed with **randomizeR**.

Any combination of the above methods can be used. For example, a simulated reference set can be used to assess the distribution of the exact rejection probabilities. The combination of simulated error rate with simulated reference set is usually used in the literature. For small sample sizes, the combination of exact reference set with distribution of exact error probabilities yields most accurate results.

All sampling algorithms use R's standard random number generator, the Mersenne-Twister (R Core Team 2016).

3. The **randomizeR** package

3.1. Overview

The **randomizeR** package covers two closely connected purposes: The generation of randomization sequences and the assessment of randomization procedures according to the aforementioned criteria. The previous chapter was dedicated to introducing the basic terms and literature from the field. In the present chapter, we show how **randomizeR** addresses these purposes. The current version 1.3 of **randomizeR** is based on R 3.3.0. It can be loaded in an R session via:

```
R> library("randomizeR")
```

All the main components of **randomizeR** are implemented using the S4 object oriented system.

3.2. Generating randomization sequences

There are two main purposes for the generation of randomization sequences. The first purpose is the generation of a single sequence for the allocation of patients in a clinical trial. The second purpose is the generation of multiple sequences in order to assess the properties of a randomization procedure. Both purposes can be regarded as functions that use the randomization procedure itself as basis for their behaviour. They are therefore implemented as methods that take an object representing the randomization procedure as input.

Representing randomization procedures

randomizeR implements randomization procedures as subclasses of the **randPar** class. For example, an object representing Complete Randomization with sample size $N = 10$ is generated by

```
R> N <- 10  
R> (params <- crPar(N))
```

```
Object of class "crPar"
```

```
design = CR  
N = 10  
groups = A B
```


The function `crPar` is a so-called constructor function, namely a function that generates an object of the class `crPar` and prepares it for use. The object `params` then contains all the information about the randomization procedure. Table 3 summarizes the constructor functions for the randomization procedures described in Section 2.3. In **randomizeR** an overview over the implemented randomization procedures is shown by calling `?randPar`.

Generation of a single sequence

We can use the function `genSeq` to generate a single randomization sequence for a particular clinical trial. It takes an object representing a randomization procedure as input and generates a sequence at random using this procedure. For example, the following code generates a randomization sequence using Complete Randomization with sample size $N = 10$ as above:

```
R> params <- crPar(N)
R> (rs <- genSeq(params))
```

Object of class "rCrSeq"

```
design = CR
seed = 808898100
N = 10
groups = A B
```

The sequence M:

```
1 B A A A B A B A A A
```

To ensure the reproducibility of the results and to enhance the reporting of the randomization procedure, the function `genSeq` saves all the information that was used for the generation of the randomization sequence in the object `rs` along with the randomization sequence itself.

In order to obtain the randomization sequence stored in the object `rs`, we can use the function `getRandList`:

```
R> getRandList(rs)

      [,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10]
[1,] "B"  "A"  "A"  "A"  "B"  "A"  "B"  "A"  "A"  "A"
```

The randomization sequence and the other information stored in the object `rs` can conveniently be saved to a `.csv` file by using the `saveRand` function:

```
R> saveRand(rs, file="myRandList.csv")
```

Figure 1 in Section 2.3 shows the random walk of the randomization sequence `rs`. This figure can be generated using the function `plotSeq` in **randomizeR**:

```
R> plotSeq(rs, plotAllSeq = T)
```

Randomization procedure	Constructor function	Parameters
Complete Randomization (CR)	<code>crPar(N)</code>	N sample size
Random Allocation Rule (RAR)	<code>rarPar(N)</code>	N sample size
Permuted Block Randomization (PBR)	<code>pbrPar(bc)</code>	bc block constellation
Rand. Permuted Block Randomization (RPBR)	<code>rpbrPar(N, rb)</code>	N sample size rb random block lengths
Truncated Binomial Design (TBD)	<code>tbdPar(bc)</code>	bc block constellation
Rand. Truncated Binomial Design (RTBD)	<code>rtbdPar(N, rb)</code>	N sample size rb random block lengths
Maximal Procedure (MP)	<code>mpPar(N, mti)</code>	N sample size mti max. tolerated imbalance
Big Stick Design (BSD)	<code>bsdPar(N, mti)</code>	N sample size mti max. tolerated imbalance
Efrons Biased Coin Design (EBC)	<code>ebcPar(N, p)</code>	N sample size p biased coin probability
Chen's Design (CHEN)	<code>chenPar(N, mti, p)</code>	N sample size mti max. tolerated imbalance p biased coin probability
Generalized Biased Coin Design (GBCD)	<code>gbcdPar(N, rho)</code>	N sample size rho balance factor
Adjustable Biased Coin Design (ABCD)	<code>abcdPar(N, a)</code>	N sample size a balance factor
Bayesian Biased Coin Design (BBCD)	<code>bbcdPar(N, a)</code>	N sample size a balance factor
Wei's Urn Design (UD)	<code>udPar(N, ini, add)</code>	N sample size ini initial urn composition add adjustment in each step
Hadamard Randomization (HADA)	<code>hadaPar(N)</code>	N sample size

Table 3: Randomization procedures included in **randomizeR**.

The function `genSeq` can generate randomization sequences for all randomization procedures from Table 3. The function `genSeq` has a method for each randomization procedure. For all randomization procedures, its output is an object of a class extending the class `randSeq`.

Generation of a set of sequences

Randomization procedures can be assessed based on the set of sequences they produce (see Section 2.4). `randomizeR` provides two ways to generate multiple randomization sequences from a specific procedure.

For small sample sizes $N \leq 24$, we can use the function `getAllSeq` to generate the complete set of randomization sequences. It takes an object representing a randomization procedure as input and calculates the complete set of randomization sequences of that procedure. For example, in the above case of Complete Randomization with sample size $N = 10$, we run the statement

```
R> (allSeqs <- getAllSeq(params))
```

Object of class "crSeq"

```
design = CR
N = 10
groups = A B
```

The first 3 of 1024 sequences of M:

```
1 A A A A A A A A A A
2 B A A A A A A A A A
3 A B A A A A A A A A
...
```

to get the complete set of $2^{10} = 1024$ sequences. Note that the function `getAllSeq` does not support the random block designs RPBR and RTBD or the Hadamard Randomization, because no algorithms have been established in the literature.

In those cases where the enumeration of the complete set of sequences is computationally intensive or algorithmically not feasible, the function `genSeq` can be used to generate a simulated reference set. For example for sample size $N = 50$ and Complete Randomization, a simulated reference set of size $r = 10,000$ is generated by

```
R> N <- 50
R> params <- crPar(N)
R> (randomSeqs <- genSeq(params, r = 10000))
```

Object of class "rCrSeq"

```
design = CR
```

```
seed = 1034131350
N = 50
groups = A B
```

The first 3 of 10000 sequences of M:

```
1 B  A  A  A  B  A  A  A  A  B  ...
2 B  A  A  A  B  A  A  B  B  B  ...
3 B  B  B  B  A  B  A  A  B  B  ...
...
```

The parameter `seed` can be passed to `genSeq` to ensure the reproducibility of the results.

As `genSeq` samples randomization sequences with replacement and with the true probability of occurrence of the randomization procedure represented by `params`, the result may contain duplicates. More probable sequences will occur more frequently.

randomizeR provides the function `getProb` for the computation of the true probability of occurrence randomization of sequences. `getProb` takes any object that inherits from `randSeq`:

```
R> p <- getProb(allSeqs)
R> head(data.frame(Sequences = myPaste(getRandList(allSeqs)),
+ Probability = round(p, 6)))
```

	Sequences	Probability
1	AAAAAAAAAA	0.000977
2	BAAAAAAAAA	0.000977
3	ABAAAAAAAA	0.000977
4	BBAAAAAAAA	0.000977
5	AABAAAAAAAA	0.000977
6	BABAAAAAAAA	0.000977

If applied to an object resulting from `getAllSeq`, the resulting probabilities will always sum up to one. In contrary, if applied to `genSeq`, the sum of the probabilities will not equal one, because typically, the set of sampled sequences is only a subset of the complete set of sequences. Note therefore that, in a simulation, the sampled frequency of a randomization sequence is used instead of its true probability of occurrence. Due to the nature of the sampling algorithms, the sampled frequencies converge to the true probabilities if the sample is large enough.

3.3. Assessing randomization procedures

Most of the assessment criteria in Section 2.2 depend on the assumption of normally distributed responses according to Model 1. Assume that both treatments have equal expectation $\mu_A = \mu_B = 0$ and variances $\sigma_A = \sigma_B = 1$. Then we can use the function `normEndp` representing the normal endpoint to pass these assumptions to **randomizeR** by setting

```
R> muA <- muB <- 0
R> sigmaA <- sigmaB <- 1
R> normalEndpoint <- normEndp(mu = c(muA, muB), sigma = c(sigmaA, sigmaB))
```

Criterion	Constructor Function	Parameters
Chronological Bias	<code>chronBias(type, theta, method)</code>	<code>type</code> of trend <code>theta</code> strength of trend <code>method</code> of assessment
Selection Bias	<code>selBias(type, eta, method)</code>	<code>type</code> of guessing strategy <code>eta</code> selection effect <code>method</code> of assessment
Correct Guesses	<code>corGuess(type)</code>	<code>type</code> of guessing strategy
Imbalance	<code>imbal(type)</code>	<code>type</code> of imbalance
Combined Bias	<code>combineBias(selBias, chronBias)</code>	<code>selBias</code> object <code>chronBias</code> object
Power loss due to imbalance	<code>setPower(d, method)</code>	<code>d</code> detectable effect <code>method</code> of assessment

Table 4: Criteria for the assessment.

The class `endpoint` provides flexibility for the extension to other endpoints. Currently, only normal endpoints are available.

`randomizeR` implements the criteria for the evaluation of randomization procedures as subclasses of the class `issue`. For example, an object representing the exact rejection probability in the presence of chronological bias due to linear time trend that has a strength of $\vartheta = 1$, is generated by

```
R> (cb <- chronBias(type = "linT", theta = 1, method = "exact"))
```

Object of class "chronBias"

```
TYPE = linT
THETA = 1
METHOD = exact
ALPHA = 0.05
```

The parameter `method` indicates whether the exact distribution of the type-I-error rate should be calculated or whether the test decision should be simulated by generating responses that are influenced by the trend (`method = "sim"`). The function `chronBias` is a constructor function for objects of the class `chronBias`. The object `cb` contains all the information about the bias. Table 4 summarizes the constructor functions for all the criteria of assessment presented in Section 2.2. In `randomizeR` an overview over the implemented assessment criteria is shown by calling `?issues`.

Assessment of a randomization procedure

The `randomizeR` package includes the function `assess` to evaluate the behavior of a randomization procedure with respect to one or more of the criteria from Section 2.2.

For example, if we want to evaluate the behavior of the Big Stick Design with sample size $N = 12$ and imbalance tolerance $mti = 2$ with respect to chronological bias, selection bias, and power loss given a difference in group means $d = 1.796$, we may call:

```
R> N <- 12
R> mti <- 2
R> bsdSeq <- getAllSeq(bsdPar(N, mti))
R>
R> d <- 1.796
R> sb <- selBias("CS", eta = d/4, method = "exact")
R> cb <- chronBias("linT", theta = 1/N, method = "exact")
R> pw <- setPower(d, method = "exact")
```

The function `assess` yields the true rejection probability for each criterion and each randomization sequence.

```
R> (Assessment <- assess(bsdSeq, sb, cb, pw, endp = normalEndpoint))
```

Assessment of a randomization procedure

```
design = BSD(2)
N = 12
K = 2
groups = A B
```

The first 3 rows of 972 rows of D:

	Sequence	Probability	P(rej)(CS)	P(rej)(linT)	power(exact)
1	BBABABABA ...	0.004	0.045	0.072	0.789
2	BABBABABA ...	0.002	0.042	0.066	0.789
3	ABBBABABA ...	0.002	0.039	0.062	0.789
	...				

In the case of the Big Stick Design with sample size $N = 12$ and maximum tolerated imbalance $mti = 2$, there are 972 possible sequences. The first column of the assessment corresponds to the randomization sequence and the second to its probability of occurrence of the sequence. The following columns correspond to the criteria `sb`, `cb` and `pw` passed to `assess`. The notation `P(rej)(type)` refers to the probability of rejection in the presence of the given `type` of bias. The column `power(exact)` gives the exact power of each randomization sequence. Any number of assessment criteria can be passed to `assess`. For the criteria `imbal` and `corGuess` the endpoint `endp` is not relevant and can be omitted.

The `summary` of the assessment shows the important characteristics of the distribution of the allocation sequences such as mean, standard deviation, minimum, maximum and the quantiles for each criterion:

```
R> summary(Assessment)
```

	P(rej)(CS)	P(rej)(linT)	power(exact)
mean	0.056	0.046	0.795
sd	0.013	0.006	0.006
max	0.109	0.072	0.800
min	0.034	0.042	0.789
x05	0.037	0.042	0.789
x25	0.048	0.042	0.789
x50	0.054	0.044	0.789
x75	0.062	0.048	0.800
x95	0.079	0.058	0.800

For example, the five percent quantile `x05` of the probability of rejection in the presence of a linear time trend `linT` is 0.042. Note that, until now, only the mean value of each criterion has been studied in the literature.

Comparison of randomization procedures

randomizeR provides the function `compare` for the comparison of several randomization procedures with respect to one of the criteria from Section 2.2. For example, assume we are in the same setting as above ($N = 12$) and want to compare the Big Stick Design, the Maximal Procedure with $mti = 2$ and the Permuted Block Randomization with block size four with respect to their susceptibility to selection bias. We can partly recycle the previous code and set the parameters for the other randomization procedures we want to compare:

```
R> mpSeq <- getAllSeq(mpPar(N, mti))
R> bc <- rep(4, N/4)
R> pbrSeq <- getAllSeq(pbrPar(bc))
```

Then the following code compares the aforementioned procedures with respect to selection bias:

```
R> (Comparison <- compare(sb, bsdSeq, mpSeq, pbrSeq, endp = normalEndpoint))
```

Comparison for P(rej)(CS)

	BSD.2.	MP.2.	PBR.4.
mean	0.056	0.072	0.082
sd	0.013	0.015	0.015
max	0.109	0.109	0.109
min	0.034	0.040	0.050
x05	0.037	0.050	0.061
x25	0.048	0.061	0.072
x50	0.054	0.072	0.079
x75	0.062	0.079	0.099
x95	0.079	0.100	0.103

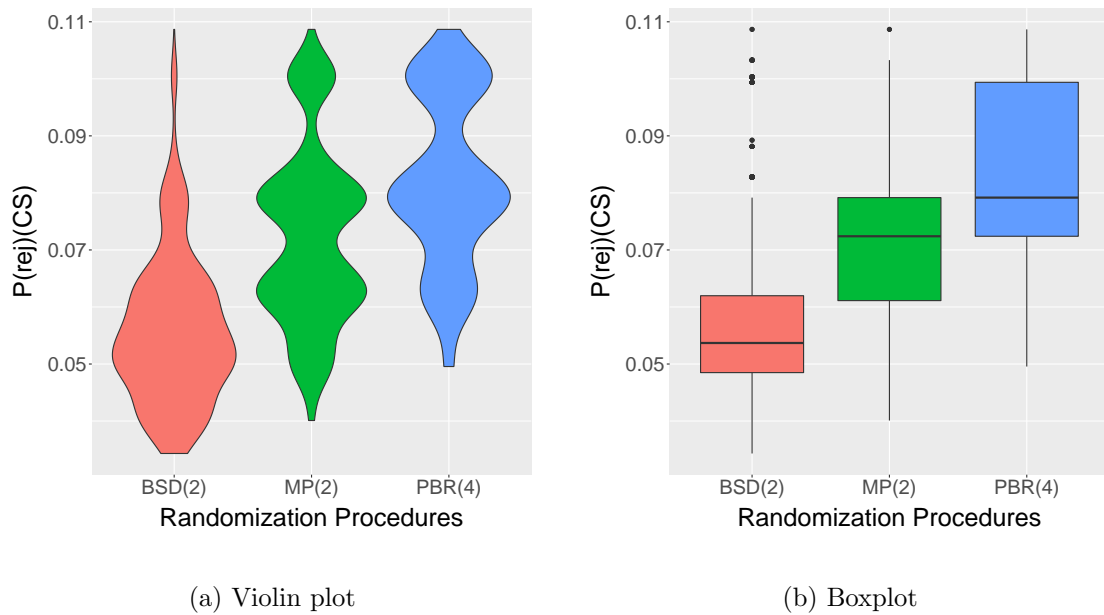


Figure 2: Comparative visualization of the distribution of the type-I-error probability under the influence of unobserved selection bias for BSD(2), MP(2) and PBR(4).

The distribution of a criterion for a particular randomization procedure can be visualized and compared between different randomization procedures via boxplot (Figure 2b) or violin plot (Figure 2a):

```
R> plot(Comparison)
R> plot(Comparison, y = "boxplot")
```

For the generation of boxplot and violin plot, we used the functions `geom_boxplot` and `geom_violin` of the R package **ggplot2** proposed by Wickham (2009).

4. Summary and further research

randomizeR is an R package that facilitates the generation of randomization lists for a large number of randomization procedures and makes the assessment of randomization procedures with respect to various criteria possible. The package currently implements fifteen randomization procedures and six criteria for the assessment of the procedures. It assists researchers at the design stage of a clinical trial by letting the choice of a randomization procedure and the implementation of the design go hand in hand.

We are working towards extending **randomizeR** in various directions. The object oriented approach makes it easy to add new randomization procedures and assessment criteria. A unified assessment criterion may be included to uniformly judge the suitability of a randomization procedure based on various criteria. The models may be extended to other endpoints such as time-to-event data, or to more than two treatment groups. Finally, randomization tests may be implemented to enable randomization based inference independent of parametric assumptions.

Name	No	Doc	Protocol	A&C	License	Platform
randomizer.org (?)	1	u	y	n	pf	Web
randomization.com (?)	3	X	n	n	pf	Web
GraphPad QuickCalcs (?)	1	u	n	n	pf	Web
Sealed Envelope (?)	1	u	y	y	pc/pf	Web
OpenEpi (?)	1	t	n	n	o	Web
randomizer.at (?)	3	X	n	n	pc/pf	Web
WinPepi (?)	2	u	n	n	pf	Windows
RITA (?)	4	X	y	n	pc	Windows
Randomization (?)	1	X	n	n	pf	Windows
Clinstat (?)	2	u	y	n	pc	MS-Dos
blockrand (Snow 2013)	1	u	n	n	o	R
experiment (?)	2	t	n	n	o	R
randPack (?)	2	t	n	n	o	R
RALLOC (?)	1	u	n	n	pc	Stata
Randomizer for Clinical Trial (?)	1	X	n	n	pc/pf	iOS

Table 5: Results of a google search to identify software tools for randomization in clinical trials, evaluated by the number of included randomization procedures (No) and the availability of documentation (Doc), randomization protocol, assessment and comparison (A&C), the license and the platform of the software tool.

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A. Review of Software packages

We conducted a google search with the keywords ”+randomization +software clinical trial”, ”+randomization +service clinical trial” and ”+randomization +package clinical trial” that yielded a total of 310 results including many duplicates. We only considered software that provided access over the world wide web, e.g. via download or via a browser-based web application. We refer to this software as ”tools”. Results that required getting in touch with the authors in order to access the tool were excluded. We also excluded tools that only included response- and covariate-adaptive randomization procedures. Fifteen software packages were left from the initial 310 results. Clearly, not all software tools on the world wide web were identified in this search, but we are confident that we captured a substantial part. The results of the literature review are shown in Table 5. We used the following criteria and abbreviations for the evaluation:

Number of available procedures (No) The number of restricted randomization procedures supported by the software tool.

Documentation (Doc) The type of documentation provided by the software tool, such as

manuals for the end user (u), technical documentation of codes and algorithms including references to relevant literature (t), or no documentation freely available on the website (X).

Protocol The randomization protocol with the details of the randomization procedure and randomization sequence can be saved to a file (y/n).

Assessment and comparison (A&C) Randomization procedures can be assessed and compared with respect to criteria from the literature (y/n).

License The license the tool is published under: open source license (o), proprietary but available free of charge (pf), proprietary and commercial (pc), or proprietary and commercial, but a light version is available free of charge (pc/pf).

Platform The computing requirements necessary to run the software tool.

The most striking result from Table 5 is the low number of randomization procedures supported in the available software tools. Twelve out of fifteen tools provide only one or two randomization procedures. In most cases, these are permuted block randomization or complete randomization. None of the tools provide more than four randomization procedures. Despite being crucial for statisticians as well as clinical trialists, the state of the available documentation is poor. Only three software tools implement detailed technical documentation, while seven of the remaining tools provide manuals for the end user. However, both types of documentation are needed in order to ensure the correct usage and functionality of the tools. The other five tools did not provide or reference any documentation on their website. Without documentation on the method used to generate the random allocation sequence, the type of randomization and details of any restriction as recommended by the CONSORT 2010 Statement (?), the possible effects of bias on the data cannot be assessed, and the validity of the trial can be compromised. Only four tools provided the functionality to generate and save a protocol of the randomization that includes this information.

One of the investigated software tools allowed the assessment of the implemented randomization procedure. Namely, it allows the assessment of the average amount of final imbalance using permuted block randomization with random block sizes by simulation. The remaining tools do not implement any type of assessment or comparison of randomization procedures, making it hard for the user to choose a randomization procedure based on objective criteria.

Another important point for the availability of a tool is its license. Only four of the investigated software tools were published under open source license. The remaining eleven tools are proprietary and therefore restrict the inspection, modification and redistribution of the programme code, which results in tools that are a black box for their users. In addition, three of the proprietary tools provide only a commercial version and might not be accessible to all possible users.

Lastly, five of the tools rely on a specific operating system. Only the web-applications, the R packages and the stata module have the advantage of running independent of the operating system. Clearly, less system requirements lead to better availability for a larger variety of users.

In conclusion, none of the existing software tools combines a large number of randomization procedures with extensive documentation, availability of randomization protocols and

assessment of randomization procedures as well as accessibility via open source license and cross-platform availability.

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