Big Stick Design Within Arbitrary Boundaries Minimizes the Selection Bias in an Open-Label Trial

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Abstract
The investigator in a randomized open-label single-center trial knows the treatment assignments of all randomized subjects and based the knowledge of the allocation procedure used in the trial can often make a guess regarding the treatment to be assigned to the next subject. This allows the investigator to introduce the selection bias in the study results [Rosenberger and Lachin, 2016] by allocating subjects with a better prognosis to a specific treatment group. Blackwell and Hodges (1957) demonstrated that the truncated binomial design of the size N (an even number), where subjects are allocated at random with probability ½ until one of the treatment arms reaches the full size of N/2 subjects and the remaining subjects are allocated to the opposite arm, minimizes the selection bias among all 1:1 allocation procedures that assign N/2 subjects to each treatment. We expand this fact to allocation spaces other than an N×N square by demonstrating that among all two-arm equal allocation procedures with an arbitrary allocation space the selection bias is minimized with the procedure that allocates subjects at random with probability ½ as long as allocation to both treatments is allowed.

Key Words: selection bias, big stick design, allocation procedure, randomization, guessing strategy, allocation space

1. Introduction

The investigator in a randomized open-label single-center trial knows the treatment assignments of all randomized subjects and based on that and the knowledge of the allocation procedure used in the trial can often make a guess regarding the treatment to be assigned to the next subject. With that, the investigator can allocate subjects with a better prognosis to a specific treatment group, introducing the selection bias in the study results [Rosenberger and Lachin, 2016].

The extent of the selection bias depends on the allocation procedure and the guessing strategy employed by the investigator. In this paper we will consider only two-arm equal allocation procedures symmetric with respect to the two treatments. Such symmetry is a common feature of 1:1 allocation procedures; it also ensures that the unconditional allocation ratio is 1:1 regardless of the order of the subject's enrollment.

When a 1:1 allocation procedure that preserves the unconditional allocation ratio at every allocation is designed to have exactly equal group sizes at the end of the allocation, the highest selection bias is achieved with the directional strategy [Kuznetsova, 2017]. The directional strategy means guessing the treatment that has the conditional probability of >1/2 to be assigned to the next subject [Berger, 2005]. When both treatments have conditional probabilities of ½ to be assigned next, no selection bias can be introduced at the next allocation and the guess is made by a toss of a fair coin. When the allocation sequence is not required to end with exactly equal treatment group sizes, the directional strategy remains a practical choice.

For most restricted 1:1 allocation procedures the conditional probability of the underrepresented treatment is >1/2. For such procedures the directional strategy coincides with the convergence strategy that dictates guessing the underrepresented treatment. For some 1:1 allocation procedures the conditional probability of the underrepresented treatment is either >1/2 or is equal to ½ (as is the case with the big stick design until the boundary is reached). In this case, the convergence strategy results in the same selection bias as the directional strategy. While the directional strategy requires the knowledge of the allocation procedure, the convergence strategy does not. Since for most 1:1 allocation procedures the directional strategy results in the same selection bias as the convergence strategy, the directional strategy is often not even mentioned in the context of the equal allocation. However, when the underrepresented treatment is given conditional probability <1/2, the directional strategy differs from the convergence strategy and is applied to maximize the selection bias.

Blackwell and Hodges (1957) demonstrated that the truncated binomial design of the size N (an even number), where subjects are allocated at random with probability ½ until one of the treatment arms reaches the full size of $N/2$ subjects (the remaining subjects are allocated to the opposite arm), minimizes the selection bias among all 1:1 allocation procedures that assign $N/2$ subjects to each treatment. The selection bias is derived in a context when the investigator knows the allocation procedure employed in the study.

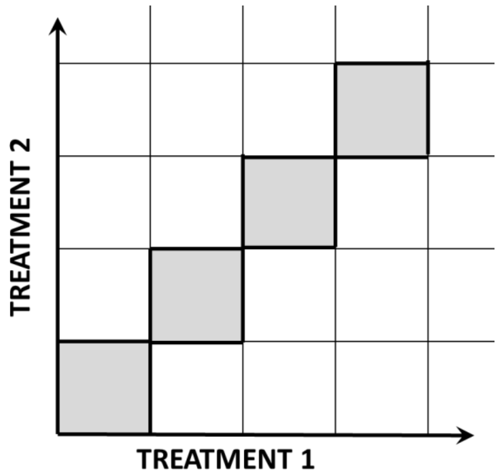
While Blackwell and Hodges (1957) solved the problem of minimizing the selection bias among the procedures with the allocation space restriction that the group sizes are equal to $N/2$ each, the problem remained unsolved for other restrictions on the allocation space.

In Section 2 we will demonstrate that for arbitrary restrictions on the allocation space the selection bias is minimized when subjects are allocated at random with probability ½ as long as the allocation to both treatments is allowed. We will introduce concepts and notation used throughout the paper in Section 1. A brief discussion completes the paper.

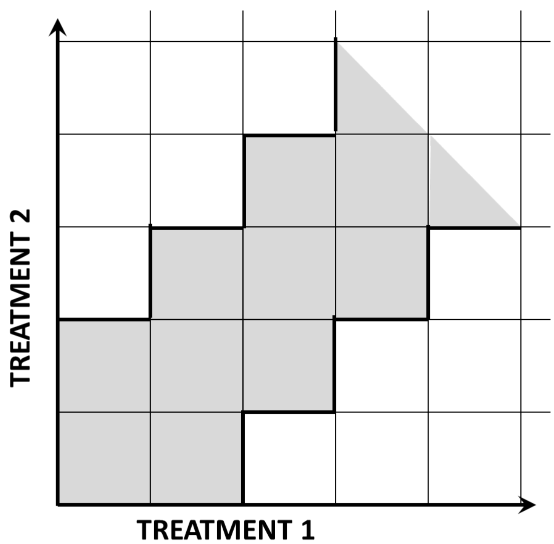
2. Concepts and Notation

We will visualize an allocation sequence as a path along the integer grid in the 2-dimensional space. The horizontal axis represents allocation to Treatment 1; the vertical axis represents allocation to Treatment 2. The allocation path starts at the origin and with each allocation moves one unit along the axis that corresponds to the assigned treatment. After i allocations, the allocation path ends up at the node with coordinates (N_{1i}, N_{2i}), where N_{li} is the number of Treatment l, l =1, 2, allocations within the first i allocations.

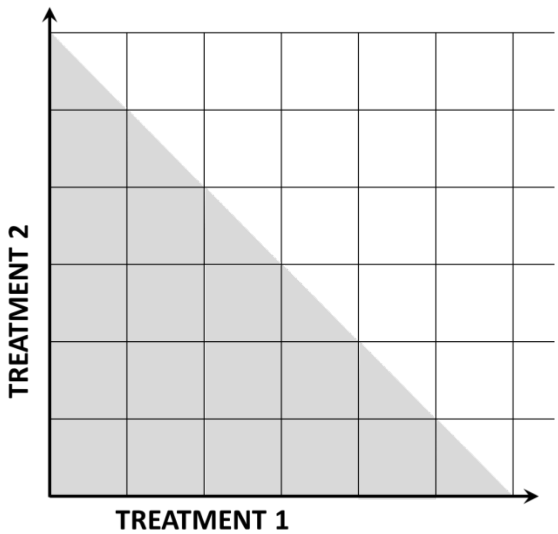
The set of nodes that can be realized with a given allocation procedure forms its allocation space. For example, for the two-arm Permuted Block Randomization (PBR) (Zelen, 1974) with the permuted block size 2, the allocation space for a study subjects is a chain of unitary squares placed along the diagonal (Figure 1a). The allocation space of the truncated binomial design of the size N is the $N/2 \times N/2$ square.



a)



b)



c)

Figure 1: The allocation space of a) PBR with the permuted block size 2 for *N*=8; b) BSD with *b*=2 for *N*=8; c) CR for *N*=6.

Soares and Wu (1982) introduced the Big Stick Design (BSD) with the imbalance intolerance parameter *b* that allocates subjects at random with probability ½ as long as the imbalance in treatment assignments is below *b*. When the imbalance of *b* is reached, the subject is allocated to the underrepresented treatment. Thus, the allocation space of the big stick design is a strip of height 2*b* on a two-dimensional unitary grid. The PBR with the permuted block size 1 (Figure 1a) is the big stick design with *b*=1. Figure 1b depicts the allocation space for the big stick design with *b*=2.

The truncated binomial design can be considered a big stick design within the boundaries of the $N \times N$ square. However, boundaries other than those of a square or a strip can be considered for a restricted allocation procedure. For example, for the permuted block design with varying block sizes [Rosenberger and Lachin, 2016] the boundaries outline a sequence of non-overlapping squares of varying dimensions. Varying the imbalance intolerance parameter as suggested by Zelen (1974) turns the allocation space into a series of overlapping squares of varying dimensions. If one if interested in keeping the balance in treatment assignments tighter at the beginning of enrollment than later on when more subjects are enrolled, the allocation space can be made narrow at the beginning and widened up as the allocation progresses.

For complete randomization of *N* subjects, the group totals N_1 and N_2 can take any combination such that $N_1 + N_2 = N$ and thus, the allocation space is a triangle depicted in Figure 1c.

The BSD can be generalized to any allocation space as the procedure that allocates subjects at random with probability ½ as long as allocation to both treatments is allowed and allocates the subject deterministically when the allocation path reaches the boundary of the allocation space. With that, complete randomization can be considered a big stick design within its boundaries.

We will call the nodes that can be realized with the allocation procedure after i allocations the nodes of generation i. We will number the nodes from 1 to m_i, where m_i is the number of nodes in generation i. We will call the probability for an allocation sequence to reside in the j-th node in generation i the resident probability of the node and denote it R_{ij}. The sum of the resident probabilities across the nodes of the same generation is 1.

Under the Blackwell-Hodges (1957) model, the selection bias is represented by the expected difference in the treatment group means in absence of a treatment effect [Rosenberger and Lachin, 2016]. In a study with 1:1 allocation of N subjects where N_1=N_2=N/2, the selection bias is proportional to the expected bias factor $E(F) = E(G) - \frac{N}{2}$, where G is the total number of correct guesses [Rosenberger and Lachin, 2016].

Let v_{1ij} denote the conditional probability of Treatment 1 allocation from the j-th node in generation i. Then as demonstrated in Rosenberger and Lachin (2016) for the convergence strategy (also true for the directional strategy), the expected bias factor is

$$E(F) = \sum_{i=0}^{N-1} \mathrm{E}\left|v_{1ij} - \frac{1}{2}\right|, \quad (1)$$

Expression (1) can be written in terms of the resident probabilities R_{ij}, j=1 to m_i, of the m_i nodes in generation i:

$$E(F) = \sum_{i=0}^{N-1} \sum_{j=1}^{m_i} R_{ij} \left|v_{1ij} - \frac{1}{2}\right| \quad (2)$$

3. Big Stick Design Minimizes the Selection Bias

Theorem 1. Among all 1:1 allocation procedures symmetric with respect to Treatments 1 and 2 and arbitrary pre-specified symmetric boundaries on the allocation space, the big stick design has the lowest selection bias when the investigator knows the allocation procedure used in the study and follows the directional strategy.

Proof. We will prove this statement by induction.

1) First, consider the smallest allocation space possible in a study with N subjects – the allocation space of the BSD with the maximum tolerated imbalance of 1 (Figure 1a). This is the only possible allocation procedure within the specified boundaries, and thus, has the lowest possible selection bias.

We will show that as this allocation space is expanded to a larger allocation space, the BSD within the expanded space continues to provide the smallest selection bias.

2) Suppose, Theorem 1 is true for the allocation space S (shaded in Figure 2) that has an open corner ADC on its boundary, so that the assignment from node A is deterministic (to Treatment 2). Node B one step to the right from node A does not belong to S. We will show that Theorem 1 is also true for the allocation space S_1 formed by adding node B to the allocation space S (Figure 2).

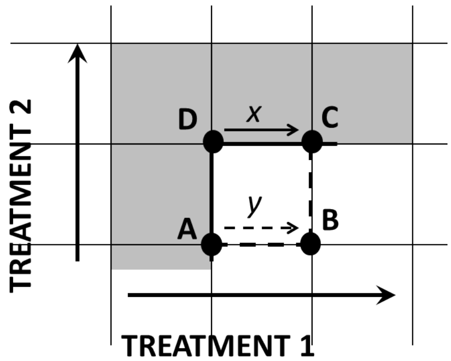


Figure 2: The open corner *ADC* on the low boundary of the allocation space *S* (shaded area) and node *B* added to space *S* to extend it to space S_1.

Let Procedure 1 be a 1:1 allocation procedure on space S_1. Denote by *x* the conditional probability of Treatment 1 allocation from node D and by *y* the conditional probability of Treatment 1 allocation from node *A* with Procedure 1 (Figure 2). Let us denote by R_A, R_B, R_C, and R_D the resident probabilities of the nodes *A*, *B*, *C*, and *D*, respectively, with Procedure 1. As can be seen from Figure 2, $R_B = yR_A$ and $R_C = yR_A + xR_D$.

Let Procedure 2 be the allocation procedure on the allocation space *S* generated from Procedure 1 by making the allocation from node *A* to node *D* deterministic. With Procedure 2, the resident probability of node *D* becomes $R_D(2) = R_D + R_B = R_D + yR_A$ and the conditional probability of Treatment 1 allocation from node *D* becomes $R_C/(R_B+R_D)$. The resident probabilities of nodes other than *B* and *D* are the same under Procedures 1 and 2. The conditional probabilities of Treatment 1 allocation for nodes other than *A*, *B*, and *D* are the same under Procedures 1 and 2.

We can also look at Procedure 1 as the procedure that is generated from Procedure 2 by allowing the allocation from node *A* to node *B* with probability *y*, $0 < y < 1$.

The expected bias factor of Procedure 1 (EBF_1) is reduced compared to the expected bias factor of Procedure 2 (EBF_2). Let us denote by γ the difference in the expected bias factors for the two procedures: $\gamma = EBF_2 - EBF_1$.

<u>*Lemma 1*</u>. For the allocation space S_1, for any value of *y*, $0 < y < 1$, $\gamma \le \frac{1}{2} R_A$; γ reaches the minimum of $\frac{1}{2} R_A$ if and only if $y = \frac{1}{2}$.

<u>*Proof of Lemma 1*</u>. From (2),

$$\gamma = \left(\frac{1}{2}R_A + R_D(2)\left|\frac{R_C}{R_{D2}} - \frac{1}{2}\right|\right) - \left(R_A\left|y - \frac{1}{2}\right| + \frac{1}{2}R_B + R_D\left|x - \frac{1}{2}\right|\right) =$$
$$= R_A\left(\frac{1}{2} - \left|y - \frac{1}{2}\right| - \frac{1}{2}y\right) + \left(R_D(2)\left|\frac{R_C}{R_{D2}} - \frac{1}{2}\right| - R_D\left|x - \frac{1}{2}\right|\right) \quad (3)$$

From (0), the second term

$$R_D(2)\left|\frac{R_C}{R_{D2}} - \frac{1}{2}\right| - R_D\left|x - \frac{1}{2}\right| = \left|xR_D + yR_A - \frac{1}{2}(yR_A + R_D)\right| - R_D\left|x - \frac{1}{2}\right| =$$
$$= \left|R_D\left(x - \frac{1}{2}\right) - \frac{1}{2}yR_A\right| - R_D\left|x - \frac{1}{2}\right| \le \frac{1}{2}yR_A \quad (4)$$

Thus, from (3) and (4)

$$\gamma \leq R_A\left(\frac{1}{2} - \left|y - \frac{1}{2}\right| - \frac{1}{2}y\right) + \frac{1}{2}yR_A = R_A\left(\frac{1}{2} - \left|y - \frac{1}{2}\right|\right) \leq \frac{1}{2}R_A \qquad (5)$$

and γ reaches its maximum at y=1/2. *EOP of Lemma 1*.

From Lemma 1, if the big stick design has the smallest EBF among all procedures on space *S* then the big stick design also has the smallest EBF on its expansion S_1 obtained by closing the open corner on the boundary of *S*.

Now we will show that the BSD also provides the smallest selection bias when an allocation space has more than a single node in the *N*-th generation.

Consider the closed corner *CDA* on the boundary of the allocation space S_2 (the shaded area in Figure 3), where *D* is the node in the last (the *N*-th) generation. Let S_3 be the allocation space obtained by adding node *B* (the node one step to the right from *A*) to *S*.

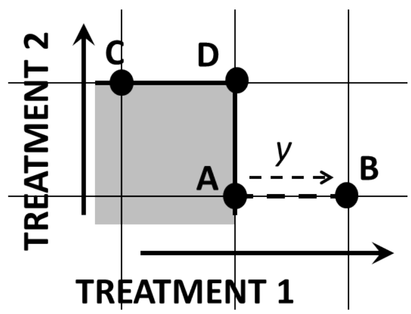


Figure 3: The closed corner *CDA* on the boundary of the allocation space S_2 (shaded area) and node *B* added to space S_2 to extend it to space S_3.

Let Procedure 3 be a 1:1 allocation procedure on space S_3, with y denoting the conditional probability of Treatment 1 allocation from node *A* with Procedure 1 (Figure 3). Let Procedure 4 be the allocation procedure on the allocation space S_2 generated from Procedure 1 by making the allocation from node *A* to node *D* deterministic. The resident probabilities of all nodes are the same under Procedures 3 and 4; the conditional probabilities of Treatment 1 allocation for nodes other than *A* are also the same under Procedures 3 and 4.

Let us denote by γ_2 the difference in the expected bias factors for the two procedures: $\gamma_2 = EBF_4 - EBF_3$.

<u>*Lemma 2*</u>. For the allocation space S_3, for any value of y, $0< y<1$, $\gamma_2 \leq ½R_A$; γ_2 reaches the minimum of $½R_A$ if and only if y= ½.

<u>*Proof of Lemma 2*</u>. From (2), the difference in the expected bias factors for the two procedures is
$\gamma_2 = \frac{1}{2}R_A - R_A\left|y - \frac{1}{2}\right| = R_A\left(\frac{1}{2} - \left|y - \frac{1}{2}\right|\right) \leq \frac{1}{2}R_A$. The difference is maximized when y=1/2.

Thus, from Lemma 2, if the big stick design has the smallest EBF among all procedures on space S_2 then the big stick design also has the smallest EBF on space S_3. *EOP of Lemma 2*.

Of note, to keep the expanded allocation space symmetric with respect to Treatments 1 and 2, when node *B* is added to the allocation space, a node symmetrical to *B* with respect to the diagonal should be added to the allocation space as well.

Starting with the chain of *N*/2 unitary squares (Figure 1a) any allocation space symmetrical with respect to Treatments 1 and 2 for an *N*-subject allocation can be built by closing the open corners on the boundary and opening the closed corners at the last generation one by one. From Lemmas 1 and 2, for every expansion of the original shape the BSD provides the smallest selection bias. *EOP of Theorem 1*.

3. Discussion.

The two-arm equal allocation procedures are often compared in the selection bias they can generate in an open-label study. It is useful to know that for the same allocation space the BSD results in the smallest selection bias. This makes the BSD the standard against which all other allocation procedures can be compared in selection bias.

References

Berger, V.W, 2005. Selection Bias and Covariate Imbalances in Randomized Clinical Trials. John Wiley & Sons: Chichester

Blackwell, D., Hodges, J.L., 1957. Design for the Control of Selection Bias. Ann. Math. Statist. 28, no. 2, 449--460. doi:10.1214/aoms/1177706973

Kuznetsova, O.M. Selection Bias in Studies with Unequal Allocation. In: Special Topics in Randomization, Masking, and Allocation Concealment. Ed. V. W. Berger, Chapman & Hall, 2017, pp.89-122.

Rosenberger, W.F., Lachin, J.M., 2016. Randomization in Clinical Trials: Theory and Practice. Second edition. John Wiley & Sons, New York

Soares, J.F., Wu, C.F.J., 1982. Some restricted randomization rules in sequential designs. Communications in Statistics – Theory and Methods. 12, 2017-2034.

Zelen, M., 1974. The randomization and stratification of patients to clinical trials. Journal of Chronic Disease. 27: 365-375