

Randomization Procedures: The Case for Strong Encryption

Abstract

Randomization ensures an appropriate allocation of patients in a clinical trial. In practice, however, it is undeniable that there are possible attempts to decipher the randomized allocation sequence. Though, we recognize that a message may get intercepted, and therefore should be encrypted, we do not seem to recognize the importance of allocation concealment. As long as we keep the allocation sequence under lock and key, it is believed that it is impervious to subversion. Of course this is folly, and the precise method of randomization should serve as the mode of encryption. Despite numerous publications that have discredited the permuted blocks procedure on the basis of its excessive vulnerability to prediction of future allocations and, therefore, selection bias, it still remains an industry standard. In this paper, we discuss the three major MTI procedures (the big stick, Chen, and maximal procedures), illustrate the numerous encryption benefits they offer over permuted blocks, and invite readers to then draw their own conclusions based on the evidence.

Keywords: Allocation concealment; Comparative effectiveness research; Maximal procedure; Permuted blocks; Randomization; Risk of bias; Selection bias

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Abbreviations: MTI: Maximum Tolerated Imbalance

Introduction

Through comparative effectiveness research in general, and clinical trials in particular, investigators gain insight into the prevention, diagnosis, and treatment of various illnesses. For this insight to be valuable to patients, the clinical trials must, to the extent possible, reflect the reality that governs the situation. The purpose of randomization in clinical trials is to create comparable comparison groups [1]. This involves minimizing vulnerability to the prediction of future allocations, and selection bias [2]. Allocations that can be predicted can also be exploited to create an unfair advantage for the preferred treatment group. That is, better responders can be enrolled for one treatment and worse responders for another [3]. It is this concern over selection bias that has led to the widespread use of allocation concealment in clinical trials [4].

The prevailing view is that so long as the allocation sequence, once prepared, is kept under lock and key, the claim of allocation concealment is valid. Though this overly simplistic version of allocation concealment is certainly necessary, it is just as certainly not sufficient [5,6]. We hope that the allocation sequence will not end up in the wrong hands, although we cannot rule out this possibility in practice [7]. Many trials are unmasked; others that are planned as masked produce a rather imperfect level of masking. By definition, this lack of (perfect) masking is tantamount to knowledge of the allocation sequence making its way to parties who are not supposed to have this information. So masking, the second line of defense, may be absent altogether, or may have holes in it. This is where we turn to the third line of defense, namely the specific method of randomization. The question we consider is what we can learn about future allocations

given complete or partial knowledge of the prior allocations that have already been made. We wish to minimize the extent to which this limited amount of information can be parlayed into additional information by predicting future allocations based on knowledge of some or all of the past allocations.

The permuted blocks randomization procedure has been amply demonstrated to lead to excessive allocation prediction [7,8]. Despite this, the permuted blocks procedure still remains the standard randomization procedure for clinical trials. This precarious state of affairs, characterized by 1) the near ubiquity of the permuted blocks procedure; 2) its major flaws; and 3) how these major flaws translate into a tremendous risk of bias, represents an ideal (and necessary) target for minimizing the risk of bias in comparative effectiveness research. Here we introduce the three major MTI (maximum tolerated imbalance) procedures, namely the big stick procedure [9], Chen's procedure [10], and the maximal procedure [11], and we note that the existence of these superior procedures renders the permuted blocks procedure obsolete and indefensible for use in actual clinical trials [12].

Three Procedures that are Based on the Maximum Tolerated Imbalance (MTI)

Big stick randomization [9], Chen's procedure [10], and the maximal procedure [11] are the three major randomization procedures that are based on the MTI, which can ensure not only comparable treatment group sizes, but also enhanced allocation concealment by minimizing prediction and, therefore, also selection bias [13]. When the MTI is set at one, the MTI procedures reduce to the permuted block design with block size two, and in general, with two treatments and 1:1 allocation, the block size used by permuted blocks corresponds to twice the value of the MTI.

All of the MTI procedures use 1:1 allocation when there is balance and a deterministic allocation when the MTI boundary is reached. But they differ in how they handle allocations when there is some imbalance, but not reaching the MTI. In this case, the big stick design uses completely random allocation as if there were no imbalance. Chen's procedure [10] uses a specified biasing probability, which does not depend on the extent of imbalance. The maximal procedure [11] is a refinement of Chen's procedure, in that the biasing probability does in fact depend on the extent of the imbalance. But unlike with Chen's procedure, the maximal procedure does not allow the user to specify the biasing probabilities. Rather, these are induced by the procedure itself, which specifies that among the set of allocation sequences adhering to the MTI condition, one is selected at random, with equal probabilities. That is, any one (admissible) sequence is as likely as any other. The basic idea is that, at any given level of imbalance $I > 0$, the odds of allocating the next patient so as to create more imbalance is simply equal to the number of sequences $n(I+1)$ that can follow to form an imbalance of $I+1$ to the total number of sequences that can follow (for an imbalance of $I-1$ or $I+1$). With obvious notation, the allocation probabilities are $n(I+1)/[n(I+1)+n(I-1)]$ and $n(I-1)/[n(I+1)+n(I-1)]$, respectively. If the MTI is reached, then no more sequences can follow to form a new imbalance of $I+1$, and therefore $I-1$ occurs with probability 100% [13].

Despite the fact that the implementation of the MTI procedure is as simple as the implementation of permuted blocks, permuted blocks procedure is still the most frequent method used to randomize clinical trials. The R-package, *randomizer*, is a tool that enables investigators to choose a randomization procedure such as Maximal Procedure or Big Stick [14]. The availability of this package provides an uncomplicated way to utilize the MTI procedures. Since the MTI procedures reduce selection bias, investigators have more effective alternatives to the permuted blocks procedure. Maximal procedure, Big Stick and Chen's overcome the drawbacks that permuted blocks present as shown in Table 1.

Comparison of MTI Procedures

Generally, as noted, the differences among these three MTI procedures are limited to how they handle allocations when imbalance exists but not enough to reach the MTI. The big stick will allocate equally, Chen's procedure will use a fixed biasing probability, and the maximal procedure is sensitive to how unbalanced the group sizes are, with more extreme biasing probabilities as this level of imbalance increases [13]. These procedures are far more resistant to prediction than is the permuted blocks procedure [15,16].

Although we prefer the maximal procedure to the other two MTI procedures, any of these three MTI procedures is a proper randomization procedure, in contrast to the fatally flawed permuted blocks procedure. The differences in performance among the three MTI procedures are dwarfed by the differences between any one of them and the far inferior permuted blocks procedure. Still, there is a sound basis for preferring the maximal procedure to the other two MTI procedures. Figure 1 illustrates this basis, and shows how the maximal procedure performs in comparison to Chen's procedure with varying biasing

probabilities (note that the big stick is just Chen's procedure with a biasing probability of 0.5). As expected, the big stick does very well against prediction based on betting odds, since it uses equal allocation so often, and this cannot be defeated by any guessing strategy. However, by doing so, it fails to encourage balance, and therefore hits the MTI barrier more often than either the maximal procedure or Chen's procedure with larger biasing probabilities. The big stick is not especially resistant to prediction based on deterministic allocations.

We see the opposite pattern with Chen's procedure with a biasing probability of 0.99. Here, balance is encouraged quite strongly, so much so that we almost never hit the MTI boundary, and so there are almost no deterministic allocations. It is worth noting that this is even more resistant to prediction based on deterministic allocations than is a design with varied block sizes. However, this procedure is absolutely terrible against prediction with betting odds, since the one doing the guessing will almost always be correct, by definition, 99% of the time. So if we were to go with Chen's procedure, then we would not recommend either extreme, 0.5 (the big stick) or 0.99. Rather, we would opt for a more intermediate biasing probability so as to arrive at a procedure which is, in some sense, mini max, at least when properly scaled. That is, we would want to simultaneously address both forms of prediction.

We notice from Figure 1 that there is one isolated dot that lies entirely beneath the Chen bias curve. This dot corresponds to the maximal procedure. We see that when we choose p so that Chen's procedure has the same level of resistance to prediction based on betting odds, the maximal procedure offers greater protection against prediction based on deterministic allocations. And when we choose p so that Chen's procedure has the same level of resistance to prediction based on deterministic allocations, the maximal procedure offers greater protection against prediction based on betting odds. This fact, in our view, establishes the maximal procedure as objectively superior to the class of Chen's procedures, including the big stick.

Conclusion

By allowing selection bias to occur, the permuted blocks procedure diminishes the purpose of randomization in clinical trials altogether. Given that the maximal procedure is superior to the permuted blocks procedure in that it controls chronological bias as well as allocation concealment, what justification can researchers provide for using the inferior method? Is this an indication that the research did not merit the use of the best research methods? If so, then is it worth publishing? Moreover, does the Berger-Exner test show any selection bias resulting from the use of the flawed procedure? If so, then what are we to make of the tainted findings? This is an important issue and has real consequences for real people and should be treated as such.

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Conflict of Interest

None.

Table 1: Differences among MTI Procedures and Permuted Blocks.

Randomization Procedures		
Differences among Randomization Procedures	MTI Procedures Big Stick, Chen, Maximal Procedure	Permuted Block Procedures
Popularity	MTI Procedures are not widely used despite their numerous advantages over Permuted Blocks	Permuted Blocks is the standard the randomization procedure for clinical trials despite its major flaws
Prediction of future allocations	MTI Procedures prevent knowledge of any future allocations since it allows an imbalance	Once all but one group has been exhausted in the block, all remaining allocations to that block will be deterministic
Selection Bias	Since prediction of future allocations is less likely to happen, selection bias is minimized	Selection bias is more likely to happen due to the vulnerability of prediction
Betting Odds	Prediction with betting odds is reduced significantly using Maximal Procedure	Predictable allocations in Permuted Blocks allow betting odds

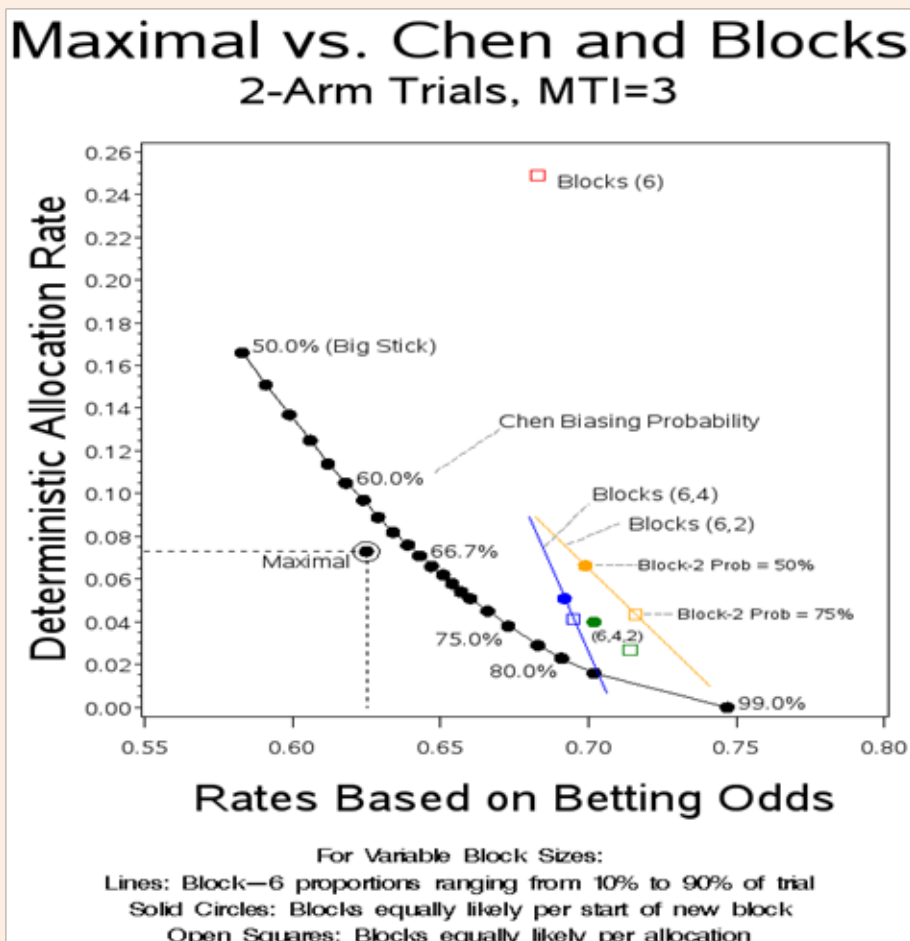


Figure 1: Comparisons of Three MTI procedures and permuted block procedures.

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