Subverting Randomization in Controlled Trials

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Recent empirical evidence supports the importance of adequate randomization in controlled trials. Trials with inadequate allocation concealment have been associated with larger treatment effects compared with trials in which authors reported adequate allocation concealment. While that provides empirical evidence of bias being interjected into trials, trial investigators rarely document the sensitive details of subverting the intended purpose of randomization. This article relates anonymous accounts of deciphering assignment sequences before allocation based on experiences acquired from epidemiologic workshops for physicians. These accounts run the gamut from simple to intricate operations, from transillumination of envelopes to searching for code in the office files of the principal investigator. They indicate that deciphering is something more frequent than a rare occurrence. These accounts prompt some methodological recommendations to help prevent deciphering. Randomized controlled trials appear to annoy human nature—if properly conducted, indeed they should.

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JAMA is stimulating increased rigor in the conduct and reporting of randomized controlled trials (RCTs).[1,2] First, it published reporting guidelines.[1] Then a subsequent Editorial[2] called for comments on those proposed guidelines and on criteria[3] published in another journal. That Editorial also endorsed the tenet of randomization being essential for reducing bias in controlled trials.[2] Is *JAMA* inflating the importance of adequate randomization?

I think not. Recent empirical evidence supports the necessity of adequate randomization.[4] We assessed the quality of randomization reporting in 250 controlled trials extracted from 33 meta-analyses and then analyzed the associations between those assessments and estimated treatment effects. Trials in which the allocation sequence had been inadequately concealed yielded larger estimates of treatment effects (odds ratios exaggerated, on average, by 30% to 40%) compared with trials in which authors reported adequate allocation concealment.[4] These results support other findings[5] and provide empirical evidence that inadequate randomization, particularly poor allocation concealment, contributes to bias in estimating treatment effects.

While we have empirical evidence of bias being interjected into trials, do investigators actually relate the delicate details of subverting the intended purpose of randomization? That has happened,[6] but given the obvious sensitivities involved, documented accounts are rare. In this article, I discuss the important elements of randomization and then present anonymous accounts of deciphering assignment sequences before allocation. Basically, since RCTs are anathema to the human spirit, we must acknowledge the human elements of this important scientific process. To help prevent deciphering, I provide a few methodological recommendations.

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WHAT IS 'RANDOMIZATION'?

Randomization, if successfully accomplished, prevents bias in allocation of participants to comparison groups. Its success depends on two interrelated processes.[4] First, an unpredictable allocation sequence must be generated based on a random procedure. Second, strict implementation of that schedule must be secured through an assignment mechanism (allocation concealment process) that prevents foreknowledge of treatment assignment.[7] Crucially, allocation concealment shields those who admit patients to a trial from knowing the upcoming assignments. The decision to accept or reject a participant must be made and informed consent obtained without knowledge of the treatment to be assigned.[8]

Traditionally, many medical researchers mistakenly consider the sequence generation process as "randomization." They properly stress generation but frequently slight concealment. Without adequate allocation concealment, however, even random, unpredictable assignment sequences can be subverted.[4,9] For example, suppose that an investigator generates an adequate allocation sequence using a random number table. However, the investigator then posts that sequence on a bulletin board, which equates to basically no allocation concealment. Those responsible for admitting participants could detect the upcoming treatment allocations and then channel participants with a better prognosis to the experimental group and those with a poorer prognosis to the control group, or vice versa.[4] Bias could easily be introduced.

Allocation concealment should not be confused with blinding. Allocation concealment seeks to prevent selection bias,

protects the assignment sequence before and until allocation, and can always be successfully implemented.[7] In contrast, blinding seeks to prevent ascertainment bias, protects the sequence after allocation, and cannot always be implemented.[7] I do not address issues pertaining to blinding in this article.

PERSONAL ACCOUNTS OF DECIPHERING ASSIGNMENT SEQUENCES

During the last 8 years, a colleague and I have conducted more than 20 epidemiology workshops for medical residents and medical school junior faculty. Each workshop included 20 to 25 participants. When we discussed allocation concealment, we asked how many of the participants had deciphered, or had witnessed someone else decipher, an assignment sequence. Typically, they responded with apprehension and silence. However, once we assured them of our lack of interest in individual names and of our preservation of everyone's anonymity, a brave soul would relate her or his experiences. Thereafter, responses usually flowed freely. When queried, more than half of the participants at each workshop related at least one instance of deciphering. This should not be interpreted as representing more than half of all the trials, however. Many participants had been involved in more than one trial, some in more than 10 trials. We do not have an accurate denominator. Nevertheless, their responses indicate that deciphering is something more frequent than a rare occurrence.

The personal accounts of those decipherings ran the gamut from simple to intricate operations. The simple operations were the most frequent and usually involved taking advantage of inadequate allocation concealment schemes. One frequently mentioned approach, taking advantage of the posting of the allocation sequence on a bulletin board, required little effort. Workshop participants admitted to adjusting allocations based on preenrollment checks of the board. Other examples of simple operations included opening unsealed assignment envelopes, holding translucent envelopes up to a regular lightbulb, feeling the differential weight of envelopes, and opening many envelopes that were not sequentially numbered until a desired treatment was found.

More elaborate operations, however, were needed to circumvent more adequate allocation schemes. For example, we have now heard of a few accounts of taking sequentially numbered, opaque, sealed envelopes to the "hot light" (an intense incandescent bulb) in the radiology department for deciphering of the assignment scheme. Apparently that works!

Workshop participants rarely implicated the more impervious allocation concealment schemes in their personal accounts of deciphering operations. Even with the good schemes, however, slight faults could develop into fatal flaws. For example, in trials using sequentially numbered drug containers, someone reported deciphering the scheme based on the appearance of the tablets and another based on the appearance of the label on the containers. Also, in trials using central randomization, we have heard a couple of accounts of physicians ringing a central number for allocation and obtaining the next few allocations all at once.

Still another workshop participant had attempted to decipher a numbered container scheme but had given up after her attempts bore no success. One evening she noticed a light on in the principal investigator's office and dropped in to say hello. Instead of finding the principal investigator, she found an attending physician who also was involved in the same trial. He unabashedly announced that he was rifling the files for the assignment sequence because he had not been able to decipher it any other way. What materialized as most curious was her response. She admitted being impressed with his diligence and proceeded to help in rifling the files. Obviously, the assignment sequence should have been kept in a locked location.

We have not asked the workshop participants why they deciphered sequences. Based on some volunteered comments, however, I have gleaned a few scanty notions. Frequently, they simply lacked knowledge of the scientific ramifications of their actions. One said that he wanted experience in vaginal rather than abdominal hysterectomies. Other documented accounts also reflect lack of knowledge.[10] The persons involved do not necessarily have unscrupulous motives.

I can speculate on a general explanation for many subversions: RCTs are anathema to the human spirit. The need for unbiased research conducted by human beings on human beings embodies a volatile mix. Investigators intellectually grasp the need but have many contradictory interests once they are immersed in a trial. They perhaps "know" the more effective treatment, so they may want certain patients to benefit or may want the results of a study to reveal what they believe to be valid. Some aspects of properly conducted RCTs, then, annoy investigators, because trial procedures attempt to impede human inclinations.

As Oscar Wilde wrote, "The only way to get rid of a temptation is to yield to it."[11] For those conducting a trial that has not incorporated proper procedures for allocation concealment, the challenge of deciphering the allocation scheme may frequently become too great a temptation to resist. Succumbing to temptation may sometimes reflect deliberate acts to alter findings. At other times, succumbing may be an innocent reflection of human inquisitiveness and ingenuity rather than scientific malevolence. Whatever the motivation, however, the effects are the same when such actions undermine the validity of the trial.

RECOMMENDATIONS

Since many allocation decipherings emanate from a lack of scientific knowledge among those conducting trials, education in the rationale and importance of trial procedures would avert many problems. More important, investigators must acknowledge the vagaries of human nature; they should establish methodological safeguards that thwart attempts to contaminate trials with bias. Particular attention to allocation concealment will prevent or deflect attempts at subversion. Moreover, medical journals should insist on adequate reporting of randomization.[1-3,7]

Regarding the generation of assignment schedules, available texts[12,13] and an entire journal issue[14] comprehensively cover the details. One aspect of generation, however, deserves greater attention. If blocked randomization is used in an unblinded trial, the block size should be randomly varied to reduce the chances that the assignment schedule will be inferred by those responsible for recruiting participants. If the block size in such a trial is not randomly varied but fixed, particularly if the size is small (eg, six or fewer participants), the block size could be unraveled. With treatment assignments becoming known after allocation, a sequence can be discerned from the pattern of the past assignments. Some future assignments could then be accurately anticipated and selection bias introduced, regardless of the effectiveness of allocation concealment.

In previous research,[4,7,15] investigators have considered the following approaches to allocation concealment to be adequate: use of sequentially numbered, opaque, sealed envelopes; pharmacy control of allocation; use of numbered or coded containers; and central randomization (eg, by telephone to a trials office). These criteria describe minimal methodological standards, yet they are met by only about one fourth of recent

trials.[7,15] Realistically, those standards should be exceeded.

Methods using envelopes are more susceptible to manipulation through human ingenuity than are other approaches and are therefore considered a less than ideal method of concealment.[9] If investigators use envelopes, they must diligently develop and monitor the allocation process to preserve concealment. In addition to using sequentially numbered, opaque, sealed envelopes, they should ensure that the envelopes are opened sequentially, and only after the participant's name and other details are written on the appropriate envelope.[16] I also recommend using pressure-sensitive paper or carbon paper inside the envelope. That transfers such information to the assigned allocation and thus creates a valuable audit trail. Cardboard or aluminum foil placed inside the envelope further inhibits detection of assignments.

Reports in which the assignment was stated to have been made by the pharmacy have been classified as having used an acceptable allocation concealment mechanism.[4,7,15] The pharmacists' compliance with proper randomization methods in these trials is unknown, however, and the precautions taken should have been reported. I am aware of instances in which pharmacists have been responsible for gross distortions of assignment schedules. For instance, one large pharmacy charged a project $150 per participant for randomization. During one weekend in the course of the trial, the pharmacy ran out of one of the two drugs being compared. The pharmacists then allocated the other drug to everyone "to avoid slowing enrollment." Investigators should not assume that pharmacists, or others involved in their trials, for that matter, are knowledgeable in RCT methods. Investigators must ensure that their research partners follow proper trial procedures.

The use of numbered or coded containers prevents foreknowledge of treatment assignment, but only if investigators take proper precautions. Authors of trial reports should specify further details of the methods. Assurances that all of the containers were of equal weight and similar appearance and that some audit trail had been established, such as writing the names of participants on the empty bottles or containers, would help readers to assess whether randomization was likely to have been concealed successfully. Similarly, although central telephone randomization is an adequate approach to allocation concealment, effective trial procedures should have been established and followed. All these details should be addressed in the trial execution and in the trial report.[1,2,7]

Investigators and methodologists often neglect one other critical element of RCT design and reporting. With all approaches, the person or persons who prepared the randomization scheme should not be involved in determining eligibility, administering treatment, or assessing outcome. That is obviously important because, whatever the methodological quality of the randomization process, such an individual would usually have access to the allocation schedule and thus the opportunity to introduce bias. Faults in this critical trial element may indeed be the crack through which much of the bias seeps into controlled trials. Nevertheless, under some extraordinary circumstances, someone may have to prepare the scheme and be involved in the trial. In those instances, the investigators must make sure that the assignment schedule is unpredictable and locked away even from the person or persons who generated it.

These recommended randomization procedures are not onerous. While trial organizers may feel some minor additional complexities, trial implementers could actually experience simplified operations. Moreover, these inexpensive procedures would account for only a small fraction of a total trial budget. As for other specific recommendations on randomization, please forward your suggestions to me as well as any additional reports of deciphering.

CONCLUDING COMMENTS

Proper randomization provides our only hope for eliminating selection bias from investigations.[17] Juxtaposed to its value, however, is the challenge human inclinations pose to RCTs. The paradox is that the reason that trials are crucial is the very reason that they are problematic. Researchers need to realize that humans, if given the opportunity, frequently subvert the intended aims of randomization. Thus, opportunities for deciphering need to be eliminated, or at least constricted, with painstaking, assiduous attention to the design and conduct of randomization schemes. Adequate allocation concealment is a vital part of that process.

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