CME

Understanding of Randomization and its reporting in Randomized Controlled Trials

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Under the present era of evidence-based healthcare in general and evidence-based medicine in particular, while searching for a new and/or more efficacious/economic intervention/drug, an optimal solution is obtained from a well-planned randomized controlled trial (RCT). For this, to avoid unexpected biases, random allocation (i.e., randomization) of considered patients in different treatment/intervention arms is mandatory. In other words, an experimental study without involving random allocation of patients between treatment arms is never an RCT. Depending on the considered research question/hypothesis/objective of the RCT, the structure of the study population, and the study design, one of the various approaches of randomization may be used. The aim of this write-up is to address a few important issues related to involved randomization under RCT.

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Introduction

A well-planned randomized controlled trial (RCT)[1-6] on a representative sample from a study population, under the present era of evidence-based health care in general and evidence-based medicine in particular, may provide optimal evidence regarding a new and/or more efficacious/economic intervention/drug. To ensure this, random allocation (i.e., randomization) of considered patients in different treatment/intervention arms is mandatory[7]. To be more specific, only an experimental study involving random allocation of patients between treatment arms becomes an RCT. As such, randomization is a basic principle of experimental design to avoid unexpected biases. Basically, it uses random numbers to allocate patients in different treatment arms and helps to secure unbiased comparisons. To be more specific, almost each of the known as well as unknown factors likely to affect the outcome becomes comparable between the arms, which pave the way for statistical inference on the treatment effects. As a matter of fact, after completion of a clinical trial, considered outcomes are compared (e.g., between intervention and non-intervention groups) to conclude one of the three possibilities: (i) intervention is efficacious; or (ii) the difference in the outcome is exclusively due to chance, or (iii) there is a systematic bias between the groups due to factors other than intervention. Randomization focuses on precluding the third possibility. In this regard, depending on the considered research question/hypothesis/objective of the RCT, the structure of the study population, and the study design, one of the various approaches of randomization may be used. The aim of this write-up is to address a few of the important issues related to involved randomization under RCT. This may help the readers to be fully aware of the unavoidable need to involve randomization in an RCT and also guide them in considering the appropriate approach in this regard.

Randomization

Under randomization, there is no place for choice. Randomization is a procedure through which study participants in an RCT are assigned to intervention groups (e.g., intervention and non-intervention groups).

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Further, in an RCT, it is also required that the investigator should not be in a position to predict group assignments in advance to avoid obvious biases. Through randomization, each participant gets a known chance of being assigned to any of the intervention groups. If randomization is used accurately, it may ensure that only intervention affects the outcome, not the other factors. In addition, the use of appropriate randomization allows the application of probability theory while analyzing and interpreting the results. In spite of being a major fundamental aspect of randomized controlled trials (RCT), it remains perhaps minimally comprehended. Non-random methods may often be used to generate allocation sequences like date of birth, record number, date of presentation, alternate days, and weekdays. Sometimes, a computerized statistical program may be used for the generation of allocation sequences, which might have been developed without involving randomness. In addition, investigators/clinicians may also decide allocation sequence themselves. Often, such non-random practices are claimed as randomization and the used approach is not specified in the proposal/protocol/report/article. As such, inappropriate use of randomization in a planned RCT makes the study a non-randomized trial.

As a matter of fact, randomization essentially comprises two connected but distinct procedures:[5-7] (i) Creation of an unpredictable randomized allocation sequence and (ii) Hiding of that sequence until assignment takes place (i.e., allocation concealment). Often it is misunderstood that randomization means to only follow an allocation list obtained from a computer personnel/biostatistician. Hence, to emphasize further, an allocation list needs to be created using one of the randomization approaches. Further, the allocation sequence has to remain hidden until the assignment is made. To be more specific, unless these isolated procedures are adopted in an RCT, there

Table 1: Random number table

5	2	7	8	4	3	7	4	1	6	8	3	8	5	1	5	6	9	6	8	1	8	0	7	8	8	7
9	7	2	4	0	2	3	6	3	1	8	5	0	2	6	0	9	9	6	9	2	1	8	5	0	3	7
5	9	8	4	3	8	9	5	2	8	4	6	4	4	2	7	5	4	4	9	2	8	1	6	9	3	2
8	1	5	6	7	7	5	7	5	3	4	8	8	0	8	8	8	6	5	2	1	2	8	2	8	9	5
3	6	5	8	3	7	8	1	0	7	9	7	5	5	9	9	9	7	3	8	9	8	3	4	5	8	3
0	1	0	0	7	5	4	1	3	0	1	9	6	6	9	9	5	5	3	2	5	6	4	6	1	6	5
5	6	6	7	2	9	3	0	9	2	4	6	1	1	7	9	1	4	0	6	0	2	5	5	2	8	3
0	2	1	8	2	3	2	0	0	6	8	3	6	5	9	7	3	4	5	3	4	5	0	5	6	6	9
9	6	7	3	8	3	2	5	4	8	3	2	5	3	3	9	5	6	3	5	2	2	1	9	5	0	3
6	8	0	5	3	3	8	1	5	2	1	2	1	4	8	3	0	5	3	7	8	9	1	4	7	7	2
9	1	9	2	9	1	8	8	4	0	9	9	0	8	7	0	4	9	3	3	9	0	3	0	4	1	7
4	6	3	6	0	3	1	6	5	3	5	9	5	4	5	1	4	0	8	7	9	6	8	4	9	9	9
2	2	7	2	4	6	0	5	7	0	5	1	6	4	7	5	0	2	2	0	1	2	6	9	5	4	9
0	2	8	6	7	2	6	9	7	6	3	0	4	2	7	5	6	2	4	8	0	1	1	1	6	3	3
1	3	3	9	3	6	2	4	0	6	0	6	8	9	9	1	9	0	2	0	3	3	2	7	7	4	6
0	7	7	1	1	5	7	2	1	3	4	4	6	1	1	2	4	7	2	4	2	4	4	2	1	6	5
3	6	4	0	7	2	2	9	3	3	2	5	5	9	1	5	3	6	3	7	8	0	7	5	8	7	1
3	3	2	5	8	8	6	2	5	0	4	6	6	0	0	5	8	3	9	0	1	5	8	0	9	3	0
6	6	3	0	0	8	8	7	4	2	3	9	5	8	1	2	6	7	1	4	8	6	9	1	9	6	9
3	2	8	9	0	4	5	7	9	0	5	2	3	5	8	7	9	1	6	4	2	7	5	2	4	3	8
5	6	6	0	1	5	1	7	2	8	7	3	5	1	6	8	9	9	6	2	4	5	5	9	2	5	6
6	1	4	3	7	7	4	1	2	8	9	1	6	2	7	7	5	2	0	4	0	4	8	6	3	9	2
9	7	7	8	5	1	4	9	6	1	8	4	0	6	3	4	3	8	3	5	2	2	5	5	5	7	6
7	6	9	5	6	1	7	5	8	6	8	2	9	2	5	9	5	3	1	0	9	8	9	8	6	0	5
5	5	7	7	5	8	3	3	1	9	1	4	3	7	9	7	7	0	3	5	5	8	8	5	6	9	2
6	5	2	8	8	7	4	5	1	6	3	2	4	0	1	6	5	6	9	2	0	7	3	6	7	3	2
8	3	6	7	3	7	5	3	9	5	9	9	8	2	5	7	2	5	8	9	4	1	3	7	2	7	5

will be no involvement of appropriate randomization in the study. Hence, the study will remain a non-RCT. Both of the distinct procedures under randomization are briefly described below:

Methods of Creating Unpredictable Randomized Allocation Sequence

There are various manual methods to be used in generating random allocation sequences, e.g., tossing a coin, throwing a dice, and mixing a set of paying cards. Although their repeated use looks practically fair, it remains clumsy and time-consuming. Further, they often become non-random in use. The use of a "table of random numbers" remains friendly, and it promises to maintain a major component of randomization, the "unpredictability of allocation sequence." It is, therefore, advisable to rely on a random number table regardless of whether doing it manually or using computer-based programs to generate unpredictable allocation sequences. On average, there is an equal number of occurrences of each digit from 0 to 9 in a random number table. Further, the pattern of digit values may not be perceived by any means. To facilitate quick referral, digits are often listed in pairs. Although often referred to either column-wise or row-wise, a random number table may be referred to randomly from any point and in any direction. Along with its friendly use, it ensures complete unpredictability. In summary, as evident from random number tables listed in almost each of the books on statistics, biostatistics, and research methodology, a random number table (e.g., Table 1) comprises random digits from 0 to 9:

The major approaches used in creating unpredictable randomized allocation sequences through random number tables are briefly described below:

Simple Randomization

Under this approach,[3,5] the unpredictable allocation list may be produced using the digits tabulated in a random number table and starting from any point. However, to be safer side, a random start even in a random number table, may serve as an added strength of this process. Let us presume that the point of random start obtained through closing eyes and putting pen/pencil on above random number table is seventh row and ninth column. In the case of two intervention arms in an RCT, moving down column-wise from the determined random start point, digits 0-4 may be assigned to the first arm (e.g., intervention: P) and remaining digits (i.e., 5–9) may be assigned to second arm (e.g., non-intervention: Q) as in Table 2.

This approach may be extended for a larger number of intervention arms. For example, in the case of three intervention arms, ignoring the digit 9, digits 0-2 may be assigned to the first arm (e.g., intervention 1: A); digits 3-5 may be assigned to the second arm (e.g., intervention 2: B) and digits (i.e., 6-8) may be assigned to third arm (e.g., non-intervention: C). Likewise, this approach may be extended to RCT involving more than three arms.

A simple randomization approach maintains the unpredictability of the assignment of each intervention completely.[3] Regardless of complexity and sophistication, there is no other random allocation approach that can outdo the unpredictability of intervention assignment and prevention of bias under this approach. Further, it is guaranteed through probability theory that with a growing sample size in the long run, the number of patients in each intervention arm may be almost the same. In spite of these advantages of using a simple randomization approach, in the case of RCTs involving a small sample size, the number of patients in intervention arms may become radically different. This problem may prevail even under large RCTs involving interim analysis, which is planned to be analyzed while a study is still in progress.

It may also be worthwhile to mention here that a randomized allocation sequence using a simple randomization approach may be replaced by a new one if there is a grave disparity in the number of patients between intervention arms. To make it more objective, it may be included under a condition in the planned proposal. For example, in an RCT involving a larger sample size, it may be stated that a generated allocation sequence may be replaced by a new one in case of an imbalance of ten or more between the arms.

Stratified Randomization

Simple randomization may sometimes generate an imbalance in some major characteristics between the intervention groups, which is expected to influence the impact of interventions differently[3]. For instance, expecting intervention effect to differ as per types of

Table 2: Randomized allocation sequence using simple randomization sequence in case of two interventions

9	0	4	5	4	5	7	7	0	1	3	5	4	9	2	2	6	8	1	1
Q	P	P	Q	P	Q	Q	Q	P	P	P	Q	P	Q	P	P	Q	Q	P	P

thyroid cancer (e.g., papillary, follicular), one needs to consider two strata, papillary and follicular. Accordingly, an unpredictable allocation sequence needs to be generated for each stratum separately that will ensure balance in relation to types of cancer between the intervention arms. Likewise, if necessary, allocation sequence may be generated for various strata considering various combinations of risk factors like age & sex, severity of disease, and centers of studies. However, as pointed out earlier, the use of simple randomization in this regard will also have similar limitations.

In addition to the above strengths, it may be worthwhile to point out a few of the precautions while deciding to use stratified randomization. To be more specific, consideration of stratification in a large-scale trial may unnecessarily complicate the process. Further, it does not have much relevance in case the interim analysis is not planned/feasible. Stratification in relation to characteristics not known to influence response to intervention is also of little use. In the absence of required resources to monitor randomization, complexity due to stratification may result in an undesired risk of errors. As such, without placing guiding principles/restrictions, stratification might just become arbitrary.

Randomization Using Random Permuted Blocks

To cope with the limitations under simple randomization, as an alternative, the randomly permuted blocks method may be used as restricted randomization to ensure an equal number of patients under each intervention arm at specific intervals, including completion of the study. As stated earlier, it will obviously help in retaining the optimal power of an RCT.[8-9] Under random permuted blocks, in the case of "I" interventions, each block of size "nI" (n≥1) will be able to provide a different random ordering of "n" assignments to each intervention. Further, in the case of small-size blocks, random number tables may be used to create a randomization list. For example, in an RCT involving only two interventions (P & Q), to begin with, a block of size two may be considered. Accordingly, digits (0–4) may be assigned to interventions in the order PQ, whereas digits (5–9) may be assigned to the interventions in the order QP (Table 3).

Likewise, in case of three interventions (P, Q & R), digit one may be assigned to block PQR; digit 2 to block PRQ; digit 3 to block QPR; digit 4 to QRP; digit 5 to block RPQ; and digit 6 to block RQP and digits 0 and 7-9 may be ignored (Table 4).

To strengthen the unpredictability further, a larger block size may be considered. To be more specific, in the case of an RCT involving two interventions (P & Q), consideration of larger block size as multiples of two (e.g., 2 X 2= 4; 2 X 3= 6; and so on) may be considered. For instance, in this case, a block size of four may be considered to assign digit 1 to block PPQQ, digit 2 to block PQPQ, digit 3 to block PQQP, digit 4 to QQPP, digit 5 to block QPQP, and digit 6 to block QPPQ; and digits 0 and 7–9 may be ignored (Table 5).

A similar approach may be used under RCTs involving more than two interventions. Further, regardless of the number of involved interventions, blocks of larger sizes may be preferred to reduce the predictability of allocation by the researchers. Also, to strengthen the unpredictability of random permuted blocks, the block size may be varied randomly from one block to the next block. In the case of RCTs involving several strata, while using the random permuted block method, generally, one may comparatively consider a small block size. Hence, to reduce allocation predictability, stratified randomization needs to be tightly restricted. At the end of each block, a record tracking of previous assignments may provide clues about the next intervention to the researcher. Further, the choice of a smaller block size has a greater risk of predictability of allocation. Hence, a researcher should not be aware of the use of blocking and its size. In summary, an innovative use of a random number table regarding simple/permuted block randomization

Table 3: Randomized allocation sequence using random permuted blocks in case of two interventions

9	0	4	5	4	5	7	7	0	1	3	5
QP	PQ	PQ	QP	PQ	QP	QP	QP	PQ	PQ	PQ	QP

Table 4: Randomized allocation sequence using random permuted blocks in case of three interventions

4	5	4	5	1	3	5	4	2	2	6	1
QRP	RPQ	QRP	RPQ	PQR	QPR	RPQ	QRP	PRQ	PRQ	RQP	PQR

Table 5: Randomized allocation sequence using random permuted blocks in case of two interventions and block size four

4	5	4	5	1	3	5	4	2	2	6
QQPP	QPQP	QQPP	QPQP	PPQQ	PQQP	QPQP	QQPP	PQPQ	PQPQ	QPPQ

with and without stratification will ensure appropriate random allocation of study participants to various intervention arms.

Equal Allocation vs. Unequal Allocation

Equal allocation[8-9] (i.e., equal sample sizes across intervention groups in an RCT) helps in minimizing the variance of estimated intervention effects, maximizing statistical power for a given total sample size, and simplifying analysis and interpretation. However, in case of significant unequal variances in the outcomes between intervention groups, consideration of unequal allocations across intervention groups might be more efficient. Further, allocating more participants to intervention groups with higher variance can improve efficiency. Also, due to ethical constraints, sometimes a lesser number of participants might be allocated to an intervention arm likely to involve more side effects. In summary, consideration of unequal allocations in various intervention arms may sometimes be unavoidable, even if this sacrifices a little statistical efficiency. For example, thyroid cancer patients being treated with conventional higher radioiodine active doses involve isolation rooms for admission. It may, therefore, be decided that the best use of resources could be achieved by randomizing a higher proportion of patients in the arms with low doses.

For the creation of an unpredictable random unequal allocation list, a random number table may be used accordingly. For example, in the case of two arms (interventions P & Q), digits 1–3 may be assigned to the intervention P group, whereas digits 4–9 may be assigned to the intervention Q group. Like in the case of random equal allocation, an unpredictable random unequal allocation list may be generated using this described assignment rule. A similar approach may be followed regarding required random permuted block randomization while using simple or stratified randomization.

Concealment of Allocation

Once an unpredictable random allocation list is ready, allocation concealment[3,6] is another component of randomization under randomized controlled trials (RCT). This is a critical and unavoidable methodological step in designing an RCT. Its non-consideration makes the RCT a non-RCT. It may be worthwhile to mention here that the mere generation of an unpredictable random allocation list does not guarantee accurate randomization. Allocation concealment is the process of preventing those involved in the registration of study participants from knowing the upcoming assignment in the randomization sequence. It safeguards against selection bias[10] by hiding the allocation sequence until a participant fulfills the inclusion criteria and consents to participate in the RCT. Without proper concealment, researchers might manipulate (consciously/unconsciously) the registration of participants to favor one intervention arm over another arm, which compromises the RCT's internal validity. Some of the commonly used methods to achieve allocation concealment are:

Opaque and Sealed Envelopes

Each of the sealed opaque envelopes is marked with an allocation sequence of the participant and contains its intervention allocation group. It has to be opened sequentially only after a participant is registered in the study. It has to be managed by an independent third party who is not part of the research team.

Central Randomization

Sometimes, for allocation concealment, intervention assignments may be managed by a centralized system, which also eliminates the possibility of local manipulation. This approach may often be useful for a multi-centric RCT. For example, under a national-level multi-centric RCT, a centralized randomization lab may be located in Delhi and connected through a hotline with each of the study centers. Once a participant is registered, the respective study center may call the centralized randomization lab to know the sequential allocation group of that participant.

Pharmacy-Controlled Randomization

Along the lines of the centralized randomization approach, the pharmacy may prepare and dispense the specific interventions based on a concealed randomization list. However, it is advisable not to involve a pharmacy in this process if it has a vested interest in developing a particular intervention.

Summary

Randomization consists of two components: first – generation of unpredictable random allocation list and second – allocation concealment. For the generation of a random allocation list using computer programs or a manual approach, the use of a random number table is mandatory. Uses of other ad-hoc approaches instead of random number tables make the process non-random. Simple randomization remains best in terms of ensuring unpredictability of allocation but may create an imbalance in the number of patients between the study arms, especially when the sample size is small. This may be a

problem even under study involving a large sample size, especially when an interim analysis is planned at specific intervals. To overcome this problem, random permuted block randomization needs to be used. This approach makes it possible to have an equal number of patients in each arm at specific time points/end of the study, which ensures the highest power of the study for a given sample size. But, while using randomly permuted block randomization, varying block sizes may be considered to minimize the risk of allocation predictability of the last patient in a block. Also, researchers need not be aware of the involvement of random permuted block randomization and the size of the blocks. Sometimes, in case of interventions involving higher toxicity and obvious need for special care of involved patients, it is advisable to use unequal allocation instead of equal allocation between the intervention arms, higher number under more toxic interventions than those under lesser toxic intervention. Its consideration may be mandatory even if there is a little loss in the power of the study.

In summary, in medical research, randomized controlled trials (RCTs) are considered the methodological standard of excellence mainly because they are designed to minimize bias and establish a causal relationship between considered intervention and outcome. With relatively minimal effort and time invested in proper randomization, medical researchers can achieve significant rewards in terms of scientific accuracy, credibility, and the overall integrity of their findings. They need to ensure the use of suitable randomization techniques to generate unpredictable allocation sequences along with allocation concealment and clearly document the approaches employed to enhance the reproducibility and credibility of their findings.[11]

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