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Randomization Systems and Technology

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Summary

When we compare treatments we want to make sure that the two groups are as alike as possible so that the comparison is a fair one. We want to be confident that any difference between the groups is due to our treatment and not to other factors that differentiate the two groups. For this reason we have to be careful about how we allocate patients into study groups, and this chapter will describe the various methods used to accomplish this.

Introduction

Is it better to ream the intramedullary canal before inserting a tibial nail or is it better not to? The best method to answer this question is to undertake a clinical trial to determine whether reaming is better than not reaming—or, more generally, if one treatment or its alternative is better. As we try to answer this question, we want to protect ourselves from making false conclusions about the effectiveness of the treatment because of biases that intrude into our study.

For example, our study may show that reamed nails lead to lower nonunion rates than nonreamed nails. However, this difference in nonunion rates may be because there are more patients with open fractures in the nonreamed group. The lower rate of nonunion in the reamed group may be due not to the treatment but to the fact that there were more patients with a high risk of nonunion (open fractures) to begin with in the nonreamed arm of the study.

To avoid this situation, and in order to make a fair comparison and be confident that the differences are due to our treatment, we must allocate subjects to the different arms of the trial in such a way that the intervention is the only differentiating factor among the groups. In other words, we must undertake a bias-free method of patient assignment.[1] By assembling comparable groups, we can ascribe with confidence any differences in outcome to the intervention alone. This is a straightforward concept in theory, but how it is implemented is a major design issue in a trial, and failure to do this with sufficient thought can jeopardize your whole study.

The response to a treatment such as an operation or drug depends on the baseline prognosis of the individual subject as it relates to the intervention and the outcome being measured. Take, for example, a study to determine differences in overall survival rates at one year after two forms of hip arthroplasty. It is obvious that the patient entering the study with renal failure, diabetes, and heart failure even before they broke their hip is likely have a shorter life expectancy than a patient without these co-morbidities; the baseline prognoses of these patients (their chances of survival after one year) are different. Now, if the study had more of these sick patients in one arm than the other, we could not be confident that the observed difference in survival was due to the intervention rather than to the differences in baseline prognosis in each of the trial arms. It is also possible that the study might fail to show a difference when one really exists; that is, one treatment really is better, but we are unable to appreciate this because of the imbalance in prognosis between the treatment groups.

These imbalances in prognosis can arise from various sources. The most important cause of imbalance, and one that we take great pains to avoid in clinical trials, is selection bias. There are a number of reasons which make it tempting to allocate subjects to either the intervention or the comparator arm: perhaps you or the resident wants more experience with one procedure over the other, or you think a particular patient will be better served by undergoing one procedure rather than another.[2,3] Allocating subjects to one arm or another in this way (even unintentionally) will lead to noncomparable groups and render the whole study unreliable.

For surgeons, it is already very difficult to undertake the "ideal" trial such as those seen in fields like cardiology, for example. It can be difficult or impossible to blind surgeons or patients, and it is also difficult to deal with the differences in surgical expertise which may account for differences in outcomes rather than the intervention itself. It can be difficult to achieve a sufficiently large sample size, and it may be difficult to assure that the co-interventions such as physiotherapy or nursing care are the same in different arms of the study.[4–6] For these reasons, it is especially important to pay attention to patient allocation, since this is one aspect of a clinical trial that can and should be done well in surgical trials and one reason it is considered an important marker of quality in surgical trials.

Methods of Patient Allocation

There are a myriad of methods to allocate patients to study arms. These methods can be broadly classified as deterministic—that is, one can *always* determine with certainty the study arm a subject will be assigned to ahead of time; or random—that is, one cannot predict which study arm a patient will be assigned to.

Deterministic Allocation

Examples of deterministic methods are study group assignment by date of birth, day of admission to hospital, or hospital numbers. Although these systems may appear to be random since people don't usually their choose birth dates, the investigator can determine with certainty which treatment assignment a participant is going to receive. Theoretically these systems may also result in unbiased comparison groups; however, the ability to predict allocation will lead to selection bias that will jeopardize the trial.[7] For example, if patients admitted on odd days receive treatment A and those admitted on even days receive treatment B, it is clear that the opportunity to choose who will be eligible to enter the trial on those days is made that much easier.

> **Key Concepts: Avoiding Selection Bias**
> To have a fair test of an intervention we must not bias the results by *selecting* subjects to treatment or control arms.

Random Allocation

The defining feature of simple random allocation is that each eligible participant in the trial has the same fixed probability of entering either study arm. Even if there is an allocation ratio greater than one (i.e., nonequal sample sizes for each arm), each individual has the same probability of entering either study arm (e.g., 1/2 for a 1:1 allocation ratio or 2/3 if there is a 2:1 allocation ratio). Most of the statistical tests of significance used in the analysis of trial data assume that the study sample is randomly selected from the population of interest.

Another feature of simple random allocation, which is of great practical importance, is that randomization balances prognostic factors among the treatment arms. Prognostic factors can be either known or unknown. Although deterministic allocation systems can deal with the known prognostic factors, only random methods can balance the unknown prognostic factors with certainty, and no other system is as unpredictable or free of bias.[8,9]

Among the random methods, allocation schemes can be divided into fixed or adaptive schemes. Fixed schemes such as simple randomization ensure that each participant in the trial has the same probability of allocation to each

arm as the next participant throughout the entire study. In adaptive schemes, the probability of being allocated to a particular arm changes during the study.

There are three types of adaptive systems to consider.

1. **Adaptive response:** Treatment-adaptive response is where the number of subjects already assigned to each study arm determines the probability of being assigned to that study arm. For example, if the starting probability of allocation is 1/2, and in the course of the study there are 15 patients in study arm A and 5 in study arm B, the probability of assignment can be altered to increase the probability of being assigned to treatment B from 1/2 to 3/4 for example. This system still maintains randomness—one cannot actually predict with certainty where the next patient is to be placed, but the probability of being assigned to a particular arm varies.

2. **Response adaptive:** The second system is response adaptive, in which allocation of one participant relies on the previous participant's response to the intervention. Thus, for example, if a person allocated to a particular treatment does well (e.g. survives), the next person is allocated to the same treatment, whereas if the person dies, the next person is allocated to the alternative treatment. A version of this is also called the "modified play the winner" rule for allocation. Although this system has been used in cases where the intervention is extreme with high mortality,[10] it has a number of disadvantages. You need to wait for a response each time before enrolling the next subject, and serious imbalances in numbers in each arm are expected, which requires very complex analysis in order to adequately interpret the results.[11] These two adaptive methods have restrictions and complexities that do not readily lend themselves to use in surgical trials and will not be discussed further, but the reader is referred to Pocock or Chow and Liu[11,12] for further details.

3. **Covariate adaptive randomization:** Covariate adaptive randomization adjusts the probability of allocation depending on the balance of *known* important prognostic factors—this is also termed the "minimization method" and is of particular interest and value in surgical trials. It has been referred to as the "platinum standard"[13] and will be discussed further.

Drawbacks of Random Allocation

It is intuitively obvious that simple randomization is the method that is least susceptible to selection bias and the most "fair," so why is this method rarely used in surgical trials?

As already stated, the major goal of random allocation is to balance prognostic factors and end up with comparable groups. However, despite the potential for simple random allocation to *eventually* balance prognostic factors, this does not usually happen in the early stages of a large trial or at any time in a small trial. It is perfectly possible for

an imbalance of prognostic factors to occur purely due to random chance. Consider the following: if two males and two females are randomized to two treatment arms A and B, the probability of both females being randomized to treatment arm B is 25%. If this occurs, clearly these will not be comparable groups. Even in relatively large studies, such imbalances can occur purely due to chance, although the likelihood of this decreases as the sample size increases and the imbalances become less of a factor (see Reality Check: Worked Examples for an illustration). These imbalances can lead to uncertain or uninterpretable results from a trial if they are of prognostically important factors. Simple random allocation can also result in un-equal sample sizes, which can present problems in statistical analysis and be a major problem if the study does not reach the intended recruitment target.

Reality Check: Worked Examples

Below are some worked examples to demonstrate how the allocation systems work for a two-armed trial. The treatment and control arms are labeled Treatment A and Treatment B. A random number generator (http://www.random.org/integers/) was used to generate the random number sequences.

Simple Randomization

We establish a rule that an even number corresponds to Treatment A and an odd number corresponds to Treatment B. Two runs of random sequences are generated.
First run generates 6 As and 5 Bs:

2	A
8	A
2	A
8	A
3	B
0	A
3	B
1	B
7	B
8	A

Second run generates 7 As and 3 Bs:

2	A
0	A
6	A
2	A
8	A
1	B
8	A
9	B
4	A
1	B

Note that in these sequences, there were imbalances in the number of subjects in each of the trial arms. If the trial terminated after the first five patients in the first run there would only be one patient in Treatment B, while there would have been no patients allocated to Treatment B in the second run.

Block Randomization

The permutations of Treatment A and Treatment B are listed below for block sizes of two or four.
For a block size of two there are two permutations:

1	AB
2	BA

For a block size of four there are six permutations:

1	AABB
2	ABAB
3	BBAA
4	BABA
5	ABBA
6	BAAB

To generate a random allocation scheme, generate a random number sequence from 1 to 6, which will be used to select the corresponding blocks as listed. The following sequence was generated: 5, 3, 1, 6, 5, 6, 4, 6, 4.
These correspond to the blocks below:

5	ABBA
3	BBAA
1	AABB
6	BAAB
5	ABBA
6	BAAB
4	BABA
6	BAAB
4	BABA

Note that, if the study were not blinded with fixed block sizes, it would be easy to predict the remainder of the allocations within the block at the end of the block; for example, after BAB, you will know for certain that the next patient will be allocated to A.
To use random block sizes of two or four, list the eight permutations:

1	AB
2	BA
3	AABB
4	ABAB
5	BBAA
6	BABA
7	ABBA
8	BAAB

A random sequence with numbers from 1 to 8 directly corresponds to above list.
Here the random sequence generated is: 6, 8, 6, 1, 4, 3, 1, 2, 2, 7.

6	BABA
8	BAAB
6	BABA
1	AB
4	ABAB
3	AABB
1	AB
2	BA
2	BA
7	ABBA

The allocation visible to the investigator is: BABABAABBABAAABABABAABBABBABAABBA.
Even if the study terminates after the 20th patient, the imbalance is half the block size at most. In this case, there are two more As than Bs at the end of the trial. With random block sizes, it is difficult to predict the next allocation as you will be unaware of which block size is being used.

Minimization: Pocock and Simon Method

The prognostic factors which are considered important are listed and categorized. In this example (**Table 3.1**) the factors are split into two categories.

So far in the study after recruiting 40 patients, the distribution of each factor is described in the table (**Table 3.2**). Note that the categories are not mutually exclusive except within each characteristic.

If the next patient to be allocated (patient #41) is a 64-year-old with an open fracture and diabetes from Hospital X, the current totals for each treatment after 40 patients are:

Total for A = 12 + 5 + 12 + 10 = 39
Total for B = 11 + 6 + 13 + 10 = 40

If this patient is allocated to Treatment A, then the total for A will become: 13 + 6 + 13 + 11 = 41 and the difference between A and B will be 1.

If the patient is allocated to Treatment B, then the total for B will become: 12 + 7 + 14 + 11 = 44 and the difference between A and B will be 5.

Therefore to minimize the differences in overall distribution of prognostic factors, the patient is allocated to Treatment A. This allocation could be with a probability of 1 (always allocated to minimize the difference) or have a rule that increases the probability to more than 0.5 but less than 1 and maintains a random component.

Stratified Randomization

If a study is stratified according to study center (X, Y, or Z) and fracture type (open or closed), the cells or subgroups formed by this combination are:

X, open	X, closed
Y, open	Y, closed
Z, open	Z, closed

Within each cell, the subjects undergo simple randomization.

Note that for only two factors there are already 6 cells. If another factor such as diabetes (classified as yes or no, i.e., two levels) was added, the number of subgroups would increase to 3 × 2 × 2 = 12.

Table 3.1 Pocock and Simon method of minimization: factors of interest

Factors of interest	Levels	
Age, years	>65	≤65
Fracture type	Open	Closed
Diabetes	No	Yes
Hospital	X	Y

Table 3.2 Pocock and Simon method of minimization: distribution of factors

Characteristic	Levels	Treatment A	Treatment B	Marginal total
Age, years	>65	8	9	17
	≤65	12	11	23
Fracture type	Open	5	6	11
	Closed	15	14	29
Diabetes	No	8	7	15
	Yes	12	13	25
Hospital	X	10	10	20
	Y	10	10	20

Problems with Random Allocation—An Example

To illustrate these problems, consider a hypothetical multicenter trial that compares two types of knee prosthesis where pain at one year is the primary outcome of interest. The trial compares the ACE Knee to the SuperDuper Knee. In the study, patients are to be recruited at different sites over a period of three years. It eventually turns out that during the study, there were changes in co-interventions (for example, a new anesthetic technique) from the beginning to the end of the study. Further, the study was terminated early at two years because of difficulties with funding and recruitment. It also became apparent during the study that one site had a very different referral pattern for the patients, with an unusually large number of patients with pre-existing chronic pain. These and other factors that affect the prognosis of the patients in relation to the outcome being measured (pain at one year) have implications for how the trial eventually plays out in terms of the balance of prognosis of patients at the end of the trial. With only simple randomization, we could have ended up with a large number of patients with chronic pain allocated to Site 1, where there were more patients allocated to the ACE Knee at the time the study was terminated early. These imbalances in prognostic factors such as the presence of chronic pain prior to surgery and the disproportionate number of patients receiving the ACE Knee at Site 1 could have rendered the whole trial uninterpretable, resulting in a huge waste of effort and resources.

As the above example illustrates, when considering allocation of subjects to the arms of a clinical trial a number of factors must be taken into consideration. The factors that should be considered when deciding upon the method of patient allocation during the design of a clinical trial are discussed below. This is not an algorithm as it is up to the individual investigators and their particular circumstances how best to balance the competing demands of these factors.

Other Considerations

Unit of Randomization

The first consideration is the unit of randomization. Will individual subjects be randomized or will it be surgeons or hospitals? It is also possible to consider randomizing one of a paired structure such as a knee, where the other serves as the control. It would make sense to randomize individual patients to an experimental or control arm of a surgical procedure, but it may make more sense to randomize physiotherapy clinics in studies examining the effectiveness of a physiotherapy treatment plan after knee replacement.

Sample Size

The number of subjects in the study is important when considering allocation strategy. As stated earlier, the most important consideration is the balance of prognosis with minimal bias. In a study with a large number of patients (more than 100 in each arm), it is likely that there will be good balance with a simple random allocation method.[9] However, when the numbers are smaller, as is often the case in orthopaedic trials where the average number is 113 ± 102,[14] there is a risk of prognostic imbalance with simple randomization.

Number and Frequency of Important Prognostic Factors

It is important to be aware of important prognostic factors and their frequency. These factors could either be related to the treatment, such as bone density in arthroplasty, or unrelated to treatment, such as the study site. It would be generally unwise to undertake a trial where the response to intervention is likely to vary widely or qualitatively, that is, some subjects improve with an intervention while others become worse. If this is the case, it is better to adjust the inclusion and exclusion criteria to make the population more homogenous.[15] If an important prognostic factor remains, then stratification based on this factor must be considered, especially if the factor is common. A special case is center effects with multicenter trials, since the study center is certain to be an important source of variation that we would want to correct for to increase the power of the study. Stratifying for center also allows dumping of a stratum (i.e., a center)[16] if a center withdraws without a major effect on the remainder of the study. Analysis will have to take into consideration the stratification undertaken at the design stage—"analyze the way you randomize."[17] However, the benefits of stratification on power disappear once a trial is above 100 or so.[9,16–18] Another important point to consider in using prognostic factors in the design of the study is the precision with which they can be classified. It is easy to determine sex or location of a fracture accurately and with minimal judgment. On the other hand, the stability of a knee joint or degree of disability is much harder to classify for use in stratification.[15,18]

Number of Arms in a Trial

In most trials, there are two arms—an intervention and a control arm. Other designs, such as multiple arm parallel trials or factorial trials, may also be considered and this will affect the methods of allocation chosen, particularly with regard to the ease of implementing the allocation scheme.

Allocation Ratio

Allocation ratios are, in general, left at a 1:1 ratio of experimental to control in two-armed parallel trials. However, this does not always have to be the case, and there are often good reasons to alter this ratio. Although statistical tests of significance are usually most powerful (able to detect a difference when one exists), with equal sample sizes among treatment arms (an allocation ratio of 0.5), the drop in efficiency is quite small until the allocation ratio moves beyond 0.7.[9,12] There are instances where it would be advantageous or even more ethical for the study as a whole to have unequal allocation.[19]

We may want to allocate patients to experiment versus control in a 2:1 ratio to improve recruitment since participants then have a greater likelihood of receiving the treatment which is expected to be "better." Alternatively, there could be more recruitment to the control arm for a second-

ary objective of the study, such as to determine the natural history of those who are untreated in a placebo or non-treatment arm. Going outside of the 1:1 ratios may lead to changes in statistical analysis and sample size calculations that need to be considered, but these adjustments are unlikely to be particularly difficult and may be worth the effort.

Length of Recruitment Period

The time frame of recruitment is important because it is possible that the subjects and their prognosis may change during the course of the trial. For example, it can be expected that perioperative care changes over time so that a patient's likelihood of certain complications decreases. This will have important implications if the recruitment period were so long that those patients recruited at the beginning of the study faced a different risk of perioperative complications than those recruited at the end of the study. It is also important to consider that there can be seasonal variations in those being recruited into a study. In studying an intervention for injuries to the anterior cruciate ligament, one would have to bear in mind that there may be differences in the type of patients presenting with these ligament injuries during the winter ski season than during the summer soccer season. A difference in the nature of the injury that follows a seasonal pattern may have an impact on the effectiveness of the intervention.

Time from Randomization to Intervention

One must consider the timing of the randomization process in relation to the intervention. It is important to analyze the results on an intention-to-treat basis in order to preserve the benefits of random allocation in the first place.[20] If there is too long a gap between allocation and intervention, it is possible for there to be significant crossover of subjects to the other arm, which will lead to difficulty in interpretation and amelioration of detectable treatment effects. This cannot be dealt with by analysis according to treatment received because of the possibility that the reason for the crossover itself may be of prognostic significance.[20] In surgical trials, it is ideal to randomize just prior to the operation as the chance of crossover is very low if the intervention immediately follows randomization, although even this may not be enough.[21] Contrariwise, if a subject is allocated to one arm a few weeks prior to the intervention because of necessary preoperative work-up or because of expertise-based trial design,[6,22] the opportunity for crossover increases.

Resources Available

All studies have to be carried out within the constraints of limited resources of both time and money. A complex allocation scheme with a large number of strata, although theoretically ideal for minimizing bias and increasing the power of the study, may be so costly in terms of resources and complexity that the entire study becomes impossible. Compromises must always be made, and these factors

must be taken into consideration.[18] Therefore, unless subjects are allocated appropriately, the validity of the whole study can come into question.

Time from Recruitment to Randomization

The method of randomization must take into account the time from recruitment of subjects to randomization. For example, if the study is addressing acute treatment of open fractures, where the time from recruitment of eligible patients to the intervention is short, the ease of accessing the randomization system is very important as randomization will have to be done during the nights and weekends. If, by contrast, the study is comparing different hip prostheses for degenerative disease, the requirement for ease and speed of implementation of randomization may be less important. In the first example, a complex system such as minimization might be too cumbersome, but in the second example this is not an issue.

Allocation Concealment

Allocation concealment, although separate from randomization, is an integral part of appropriate allocation of subjects to the treatment and control arms and must be considered carefully when deciding on randomization procedures. As mentioned earlier, even if a balance of prognosis can be achieved (at least for known prognostic factors), a deterministic allocation scheme or one that is easy to predict—for example, small and fixed block sizes with block randomization—will allow selection bias because one can predict the allocation of the next patient and thus choose not to allocate a patient to that arm. Failure in concealment of the random allocation will negate any benefits accrued by random allocation in the first place.

Allocation concealment is important to maintain blinding in blinded studies, but is arguably even more important in unblinded studies. The number of tools for reducing bias is reduced if the study is unblinded. Random allocation with adequate concealment of allocation to protect against selection bias takes on a more important role in overall bias reduction.

On this basis, some methods of randomization, such as a centralized system with random block sizes, may be preferable to others because of advantages in concealment compared to a system with a predetermined allocation schedule administered by someone at the study site.

Mechanics of How to Randomize

Despite the large number of methods available, ultimately, four methods of allocation will suit most studies likely to be carried out in orthopaedic surgery (**Table 3.3**). A summary of these methods is listed below with examples illustrated in the boxes.

Table 3.3 Comparison of allocation schemes

System	Pro	Con	Comments
Simple randomization	Least chance of bias and completely unpredictable	Can lead to imbalances in numbers in each arm and prognostic factors	Most of these drawbacks disappear with large sample sizes (>200 subjects)
Block randomization	Ensures even numbers in each arm Some protection against early stops or loss of centers	Can be predictable at the end of a block Does not balance prognostic factors	Can randomly vary sample sizes to deal with predicting allocation Central randomization will help in adequate concealment of allocation
Stratified randomization	Accounts for important prognostic factors Allows for easier subgroup analysis at a later stage	Assumes one knows that the prognostic factors are indeed important Often cumbersome if more than one or two factors are used Can lead to more strata than subjects	Center is an important stratifying factor which should be used in multicentered trials Block randomization must be carried out within each stratum, otherwise imbalance in numbers within strata defeats the purpose of stratification Must analyze with stratification factor as a covariate
Minimization	Balances prognostic factors throughout the study Can use many more prognostic factors than in stratification Very useful in small sample sizes	Not strictly random, but can add random components Possible to predict if able to keep track of prognostic factors, but this is very difficult and cumbersome	Works best with centralized computer system to both determine and conceal allocation Not well understood or well used

1. **Simple randomization:** the simplest method of allocating, analogous to a coin toss. Because one cannot create an audit trail with a coin toss, however, the use of a random number table is preferred. This is the ideal method if the study is large enough to assure balance in prognosis at the end of the trial or sometime earlier.

   Jargon Simplified: Randomization
   Randomization is the allocation of participants to groups by chance, usually done with the aid of a table of random numbers. Not to be confused with systematic allocation, quasi-randomization (e.g., on even and odd days of the month), or other allocation methods at the discretion of the investigator.[20]

2. **Block randomization:** assures similar numbers of patients in each arm of the study—but does not balance prognosis. With this method, "blocks" of allocations are randomized, where each block is one permutation of treatment arms depending on the block size. So if block size is two in a two-armed trial, there are two permutations or two blocks, while if the block size is four, there are six permutations. Smaller block sizes are easier to decipher, while too large a block size is sensitive to changes over time and in extremes and defeats the purpose of assuring equal numbers in each arm of the study.

   Jargon Simplified: Block Randomization
   Block randomization is a technique to ensure equal distribution of study subjects across treatment groups over time. Blocks of either varying (most common) or equal sizes are created such that each block contains an equal number of treatment and control (or treatment A and treatment B) allocations. The order of treatment allocation within each block is random, and the order of blocks, once they have been created, is also random.

3. **Stratified randomization:** balances known prognostic factors which may impact the outcome. We want to assure that these are distributed evenly across the trial arms, and this will theoretically decrease variability within the strata, enabling better detection of an effect. However, the gain in efficiency may not be worth the cost once the sample size becomes large. This is very useful in multicenter trials where the center will obviously be an important factor. One would want to limit the number of strata to very important factors that are frequent enough not to leave strata with too few subjects or events.

   Jargon Simplified: Stratification
   The stratification process groups individuals into strata based on an important known and measurable characteristic (such as study site or patient sex or age) to ensure that these characteristics are equally represented across the intervention groups.

4. **Minimization**[12,13,23]**:** allows for balancing of known risk factors. It can balance unknown factors to an extent, but not as much as simple randomization. The benefits of minimization do decrease after a suffi-

ciently large sample size is achieved, but this system is very good for small trials, which are the norm in surgery. Unlike stratification, minimization works at reducing the total imbalance of factors in the study rather than considering mutually exclusive subgroups, for example comparing young patients to old or young patients with open fractures to old patients with closed fractures.[23] Although theoretically it may not balance the unknown factors well, in practice it performs well enough to be considered equivalent to the other randomized allocation procedures.

Jargon Simplified: Minimization

Minimization adjusts the probability of allocation depending on the balance of known important prognostic factors.

Reality Check: Resources

1. http://www.random.org/

This online randomizer is useful for generating a variety of random numbers. Not ideal for carrying out a study, but very useful for planning.

2. http://www-users.york.ac.uk/~mb55/guide/rand-sery.htm

This is a fantastic resource to identify web-based services which can be used to allocate patients to a study.

Conclusion

Appropriate allocation to intervention and control is a fundamental aspect of clinical trials and requires a great deal of thought at the design stage. It is important to consider how the allocation sequence is generated and how it will remain concealed. Failure to address these issues will jeopardize the integrity of the study.

Regardless of the actual method of random allocation selected, the mechanics of patient allocation must ensure that the process is free of bias and must be able to provide an audit trail of patient allocation. As the techniques become more complex, these requirements also become more complex. The complexities, which must be appreciated at the outset of the trial design, illustrate the importance of obtaining sound statistical advice during the design phase of these studies as well as during the conduct and analysis stage.

The ultimate aim of a trial is to have a fair test of an intervention and appropriate allocation; that is why minimizing bias is the first step toward the goal.

Suggested Reading

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