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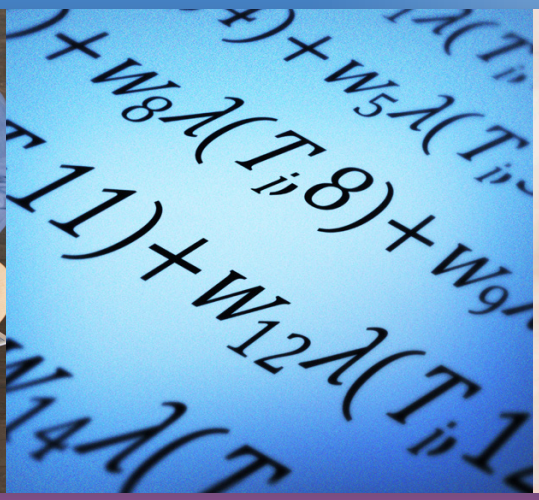

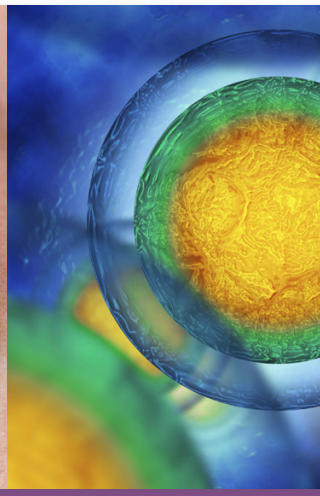

Cenduit White Paper Series: Issue 1

A Brief Synopsis of Modern Randomization Methodologies and Technologies

Randomized, double-blind clinical trials are the gold standard for adequate and well-controlled studies in modern times. However, prior to the late 1940s, randomization and blinding were not used in medicine and as result, bias was common. For example, treatment bias was often observed as physicians would treat sicker patients with known controls, while seemingly stronger patients would receive experimental products.[1] Further, when not blinded, knowledge of a patient's treatment regimen tended to affect the level of care a healthcare worker may provide and also influenced their observations regarding improvement, adverse events and other factors.

Early Randomization Methods

In modern studies, "the most important design techniques for avoiding bias in clinical trials are blinding and randomization."[2] And for multi-center trials, a central randomization methodology should be used.[3] As recent as the early 1990s, centralized randomization was achieved by generating a list that was usually grouped into blocks and stratified by investigative site to help ensure balance, that is, that the desired number of patients in each treatment group would be achieved. The list would contain sequential numbers that corresponded to the patient kits that were provided to each site. As patients were enrolled at

> ***"The most important design techniques for avoiding bias in clinical trials are blinding and randomization."***
> *- FDA.gov*

each site, the investigator simply assigned the next sequential kit. However, the kit numbers sent to sites were often non-sequential; in such instances, sequentially numbered, tamper-evident envelopes were used. The investigator would simply open the next envelope for each new enrollment and would then assign the patient the kit number contained inside *(See Table 1).*

Table 1: Fixed List at Patient Kit Level

Site	Pt/Envelope #	Kit #	Trt
1	101	505	A
1	102	515	A
1	103	513	B
1	104	522	B

Site	Pt/Envelope #	Kit #	Trt
2	201	521	B
2	202	523	A
2	203	504	A
2	204	529	B

Table 2: Permuted Blocks

Site	Site 1	Site 2	Site 3	Site 4
Trt Order	AABB	BAAB	ABBA	BBAA

The randomization method in Table 1 has several advantages. First, it uses a permuted block method with a block size of four, each containing to A's and two B's. The permuted block helps to maintain a balanced number of patients assigned to each treatment group. Table 2 shows more detail on this design and from that diagram we can see that if each site enrolls their expected four patients, we'll have an equal number of patients in each treatment arm. The same is true if each site enrolls only one or two patients.

A second advantage is that the kit numbers appear to be rather arbitrary, making it impossible for the investigator to deduce what treatment any patient is being given based on a numbering scheme. Imagine if all the A's had kit numbers from 1000 to 1999 and all the B's ranged from 2000 to 2999. The study would be compromised, or "partially unblinded" as site staff would know which patients were on the same treatment. (A future Cenduit White Paper will address situations that can lead to unblinding or partial unblinding and how to avoid these scenarios.)

Since non-marketed study medications are very expensive to manufacture, routine waste is incredibly costly

There are also some disadvantages to supplying full patient kits to each site in blocks. In most studies, these kits contained all the study medication a patient would need for the entire trial. If, for example, the study was of a six month duration and a patient discontinued after two months, then the remaining four months of supplies usually had to be collected and sent to a destruction facility. Further, any unassigned kits were often lost in a similar manner. Since non-marketed study medications are very expensive to manufacture, such waste is incredibly costly.

Technology Brings New Benefits

By the early 1990s, biopharma companies and contract research organizations (CROs) began using technology more frequently and as a result, new methods of randomization could be used that promised to preserve study treatment balance, maintain the blind to avoid bias, minimize wasted medication and greatly improve the clinical supply chain. Interactive Voice Response (IVR) and later, Interactive Web Response (IWR) systems brought many new advances to the field of Randomization and Trial Supply Management (RTSM). Today such systems are generally referred to as Interactive Response Technology (IRT) systems and have user interfaces on the web via PC, tablet, phone and similar devices.

An important advantage of IRT is a more efficient supply chain. In the example of a six-month study cited earlier, suppose each patient visits the site once per month. Instead of sending six months of medication per patient to each site, only one or two visits worth per patient could be supplied initially. When a patient is randomized via the IRT, the investigative staff is told the pack number to give the patient for that visit. For subsequent visits, the system knows which visit packs at the site will be valid for the patient and again, tells the staff which pack to dispense. Thus, if a patient discontinues early, hardly any drug is wasted as the remaining packs at the site can still be used by other patients on the same regimen. There are many more supply chain advances that IRT delivers, but in this paper, we will focus on randomization. (A future Cenduit White Paper will focus on Trial Supply Management using IRT.) Another advantage of IRT randomization is the ability to maintain balance over the duration of a study. There are a variety of methods for doing so and these are often referred to as "minimization of imbalance" designs, or simply as "minimization." The design examples mentioned so far have been very basic, but clinical trials generally involve stratification factors, such as gender, smoking status, age and other considerations. Also, treatment ratios are not always 1:1, with two groups each receiving approximately the same number of patients. There may be multiple treatment arms, each having a different number, such as groups A, B, C and D in a ratio of 4:1:1:1. IRT is indispensable in ensuring balance across the study and across various stratification factors by intelligently managing the randomization scheme according to the design and needs of the study.

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Minimization of Imbalance Methods

A well-established method for minimization of imbalance is "biased coin."[4] This is a dynamic method, meaning that there is no fixed list and each patient is assigned a treatment group at the time of randomization based on an algorithm. The decision to use minimization may be driven by a number of factors including past experience with similar trials, requests from regulatory agencies for deeper data on specific sub-groups, best practices gained from literature research, the need to include a limited number of patients and so on. To illustrate the value of these methods, let's start with a very simple example with only two treatment groups and no stratification factors and with a ratio of 1:1. When the first patient enrolls, there is an equal chance of getting drug A or B, much like

tossing a normal coin and coming up with heads or tails. In this simple case, if the first patient is assigned drug A and the second patient gets B, we have balance and we can continue to toss the normal coin. But if both patients received drug A, we would now have an imbalance with two A's and zero B's. For the next randomization, the algorithm would weight one side of the coin to give a higher probability that it will result in drug B, thereby minimizing the imbalance. It is good practice to have guidelines in place to govern these algorithms to make sure they are not deterministic; that is to say, there must always be some element of randomness in the coin toss.[5] An 80/20 weighting is generally safe as it will minimize imbalance over time, but still has a fair level of randomness.

Of course, clinical trials rarely have such simple designs and usually have multiple treatment arms, varying treatment balance ratios, multiple stratification factors and other variables that must be considered. Even for highly complex designs, minimization methods can help to maintain balance. This is generally achieved by using formulas to calculate an imbalance score as each successive patient is enrolled and then weighting the outcome in favor of the treatment assignment that will result in the lowest imbalance score. There are many methods for calculating such a score and we will illustrate two common concepts. Consider the example in Table 3 where 15 patients

Table 3: Fixed List at Patient Kit Level

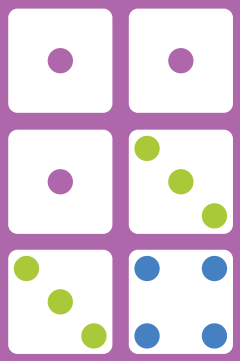
Treatment Group >	A	B	If A	If B
Gender (M:F)	5:2	3:5	6:2 = 4	4:5 = 1
Smoker (Y:N)	2:5	4:4	2:6 = 4	4:5 = 1
Age Group (Low:High)	3:4	4:4	4:4 = 0	5:4 = 1
Imbalance Scores method1/method2			16/8	14/3

have already been randomized and now the 16th arrives at the site – a male, non-smoker in the "low" age group (sub-group MNL for Male/Non-smoker/Low age group). The first method that could be used is to sum the number that would now be in the MNL group for treatment A and the same sum for treatment B. In this example, assigning the patient to A would result in a score of 6+6+4=16. Assignment to B would score 4+5+5=14. Since the score for assignment to treatment B is lower, we would weight the coin in favor of that treatment group. Another method is to sum the differences within each stratification factor. In this example, if the patient is randomized to A, the differences total as follows: ABS(6-2)+ABS(2-6)+ABS(4-4)=8. The differences for B would be: ABS(4-5)+ABS(4-5)+ABS(4-4)=3. Again, assignment to treatment B results in the lower imbalance score and we would weight the coin in favor of that treatment group.

The imbalance calculations presented so far have been rather straightforward. Suppose, though, that maintaining balance in gender is far more important than smoking status or age group. Then we could apply a weighting or multiplier to that factor in our calculation to help ensure that we continue to have approximately equal numbers of males and females in each treatment group.

Additionally, minimization methods must account for trials with multiple arms, including studies where the desired ratio of assignments is not 1:1. For example, if a study has treatments A, B and C and the desired ratio from the statistical plan is 3:2:1, the algorithm would seek to maintain balance in the stratification factors while also ensuring the treatment ratio is maintained. In this example, we could use the analogy of rolling a regular die. A one, two or three would select treatment A, a four or five would lead to B and a six would indicate treatment C. Or we could think of the die as having three sides with an "A" or one, two sides with a "B" or two and one side with a "C" *(see Figure 1)*.

Figure 1: Illustrating a 3:2:1 Ratio for Treatment Allocation ***(Illustrates an algorithm designed to assign treatments A, B and C in a 3:2:1 ratio)***



Simulation

As these randomization methods grow more complex, how can we be certain that they will maintain balance and lead to the desired ratios in treatment groups? Biostatisticians typically run a number of simulations through the study design and then analyze the behavior of the randomization schema. These simulations are based on the expected patient characteristics while also introducing some randomness to account for real-world unknowns. Using our previous example from Table 3, a simulation run may begin randomly creating patients with a 50/50 probability that the next patient will be male or female, 30/70 probability for smoker/non-smoker and 40/60 for low age/high age group. Further, some "what if" scenarios can be modeled to see what would happen if more or less randomness is introduced into the algorithms. Simulations give the statistical team insights into the likely outcomes and also give clinical teams strong evidence that the algorithms will lead to the desired results in terms of balance and treatment ratios.

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Regardless of the randomization method used, whether fixed list, permuted block or dynamic allocation, it is vital to have a provider who has the tools to monitor how the study is performing once it goes live. While simulation results provide a solid reassurance that the randomization algorithm is set up according to the needs of the study, even the best simulation techniques cannot account for every real-world factor. For example, it has been reported that 11% of clinical sites fail to recruit a single patient and many other sites under-recruit.[6] Even with a well-designed permuted block structure, as explained earlier in this paper, non-recruiting and low-recruiting sites can have an effect on treatment balance. However, ongoing monitoring of the randomization outcomes and other study "health factors" can readily pick up any anomalies so that mid-study adjustments can be made if necessary.

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Adaptive Trial Designs

An adaptive trial design is "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."[7] In other words, certain changes to the study will be made based on data analyzed during the trial with a view to getting results more quickly and at times, involving fewer patients. Any and all potential changes are clearly identified in advance in the protocol and statistical plan. Further, the design of such potential changes is generally based on results from previous trials, research on similar trials, feedback from regulators on safety issues and other considerations. There has been much information published on the topic and in this paper, we will briefly focus on a few considerations dealing with randomization.

One of the more common uses of an adaptive trial has been dose finding. For example, a study may start with several arms, perhaps at doses of 10 mg, 20 mg, 30 mg, 40 mg, 50 mg and placebo. Initially, the IRT may randomly assign patients to one of these dosing arms with equal probability. Then over time, as safety and efficacy factors are examined, either in an automated fashion or by an unblinded team, the randomization schema is altered by either changing the ratio in favor of the doses with better outcomes or by dropping an arm altogether. In this example, if the 50 mg dose was causing a high level of adverse events, it might simply be dropped and the IRT would no longer randomize patients to that dose. On the other hand, if the 10 mg dose was producing no health benefit, it too could be dropped. By the end of the trial, the majority of patients will have been randomized to one of the optimal dose levels.

Even for simple designs, it is vital to keep patients in mind and to provide them with any and all help necessary to keep them engaged in the trial

Staying with this simple example of an adaptive design, if the medication was in tablet form, would it make sense to manufacture five separate tablets for the active medication, one for each dose? Doing so could be very expensive and if we rule out use of the 10 mg and 50 mg early in the trial, all that medication would be wasted. An IRT vendor with experience in these designs can collaborate with the sponsor and the drug supply vendor to make recommendations that could easily be built into the system to optimize the entire supply chain for this, and for future studies. In this case, perhaps the team would suggest manufacturing tablets in 10 mg, 20 mg and 30 mg doses would suffice. Then each patient could be given two vials with the clear instructions to take one tablet from each vial when it is time to take their medication. Table 4 shows a simple design for this scenario. The table also shows how the IRT system could manage

Table 4: Permuted Blocks

Dose	10 mg	20 mg	30 mg	40 mg	50 mg	Placebo
Vials Distribute	1x10mg 1 Placebo	1x20mg 1 Placebo	1x30mg 1 Placebo	2x20mg	1x30mg 1x20mg	2xPlacebo
Alternative	n/a	2x10mg	1x20mg 1x10mg	1x30mg 1x10mg	n/a	n/a

alternatives if stock levels of a particular dose were running low. Of course, several other configurations are also possible and again, an experienced team can present the optimal set up and can readily implement it in the IRT. In the previous example, it is obvious that a main consideration would be minimizing the burden on patients. If it is deemed that providing two vials to each patient is too cumbersome for the given population, alternatives would be suggested. Even for simple designs, it is vital to keep patients in mind and to provide them with any and all help necessary to keep them engaged in the trial. In fact, Patient Engagement is an important and meaningful trend in clinical research and using tools, such as mobile applications to give patients timely reminders on dosing, study visits and other factors, is another way to ensure the success of a well-planned clinical trial.

Other Considerations

Once a study is carefully planned and designed, it is launched into the real world where the unexpected is bound to happen. For example, on occasion, a site may encounter a stock-out issue, meaning that the treatment to which a patient has been randomized is currently not in stock at the site. This could happen for a variety of reasons, such as part of a medication shipment being damaged or experiencing a temperature deviation in delivery. When this occurs, one solution is simply to have the patient return to the site when a new medication shipment arrives, but this is inconvenient for the patient and the site staff. A better solution may be to allow "forcing." Forcing would mean that the system automatically puts this patient onto a treatment that is currently available. Then the system would assign a higher probability that the next patient in the study would be assigned to the treatment group that was just skipped due to the stock-out. While forcing is not technically random, it is permitted by regulators as long as it is not occurring frequently. An experienced vendor can provide the necessary guidance to help ensure the quality and integrity of the study design and its execution throughout the trial's lifecycle.

On the topic of human expertise, there is a current trend toward rapid development of IRT systems and this is bringing many benefits to clinical research. Chief benefits include establishing better, more consistent standards as well as validated and reusable libraries and modules that reduce the time and burden in system testing and that lead to higher quality and reliability. However, there are many other factors involved in the design, deployment and conduct of a study and having a team of experts who understand the critical success factors, from manufacturing and packaging through accountability, returns and destruction, is essential.

Rapid development of IRT systems is important, however there are many other factors involved in the design, deployment and conduct of a study. Having a team of experts who understand the critical success factors, from manufacturing and packaging through accountability, returns and destruction, is essential

Conclusion

Randomization is a key element in the success of a trial. An effective randomization plan built into an IRT system forms the basis of an adequate and well-controlled trial that is free of bias, maintains the study blind and ensures that the desired balance and treatment allocation ratios are preserved throughout the trial. Modern systems and simulation techniques are in place that have also greatly reduced the timelines to implement an IRT system while also providing high quality, reusable algorithms with a greatly reduced validation effort. Finally, there is no replacement for a qualified and experienced team who can provide guidance on all the critical factors involved in running a successful trial.

Endnotes:

[1] Junod, Suzanne White, Ph.D., "FDA and Clinical Drug Trials: A Short History", FDA.gov.

[2] ICH E9: "Guidance for Industry: Statistical Principles for Clinical Trials", 1998.

[3] Ibid.

[4] Pocock, Stuart J.; Simon, Richard (Mar 1975). "Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial". Biometrics (International Biometric Society) 31 (1): 103–115.

[5] ICH E9: "Guidance for Industry: Statistical Principles for Clinical Trials", 1998.

[6] Getz, Ken. Enrollment Performance: Weighing the "Facts", Applied Clinical Trials, May 1, 2012.

[7] "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics", February, 2010; FDA.gov.