ISN INTERNATIONAL SOCIETY OF NEPHROLOGY | RESEARCH ACT | CLINICAL TRIALS

CLINICAL TRIALS TOOLKIT

Chapter 1 - Randomization

February 2021

1. CASE STUDY – RANDOMIZATION

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The text below is a transcript of the concepts described in the ISN-ACT Clinical Trials Toolkit. The characters and background story were added to the text to illustrate common research methods used in clinical trials. The names used refer to fictional characters making no reference to actual persons.

1.1. INTRODUCTION

Dr. Pedro Augusto, a nephrologist living in Brazil, faces a golden opportunity in his early career as researcher. Despite having conducted several non-experimental studies, he has **never been involved in a randomized clinical trial**. Now, as a young Ph.D. researcher, he's keen to do so.

An **opportunity** arose at the last World Congress of Nephrology (**WCN**) when he was introduced to **Prof. Antony Smith**.

Prof. Smith is a **senior researcher** at the University of Melbourne, Australia, currently investigating the exciting results of a new drug called X340, an SGLT2 inhibitor. This class of drugs, also called gliflozins, are believed to alter critical regulatory pathways of the nephron by essentially inhibiting the sodium-glucose transport protein 2 (SGLT2). Currently, these drugs are a promising innovation in the treatment of patients with chronic kidney diseases (CKD), especially due to diabetic nephropathy.

It was during one of the **"Building Capacity" Workshops** held at WCN that the idea of a multicenter, randomized clinical trial with the drug X340 emerged. The sessions were attended by several young nephrologists. One in particular, **Dr. Matheus Granado**, a researcher and nephrologist in Bolivia, was treating several diabetic patients fast-progressing to the late stages of CKD, despite access to conventional treatment. He knew his patients would be willing to participate in a randomized clinical trial to test new treatments.

Prof. Smith gave one of the last lectures that day. He knew it was key for him to work in **collaboration with researchers in different countries**, so he patiently addressed questions from the audience, especially regarding "external validity" and the need for a multicenter study.

As he finished highlighting his recent findings and was preparing to leave, he met Dr. Pedro Augusto and Dr. Matheus Granado. Both were eager to **discuss details of a future international study**.

1.2. RANDOMIZATION

Randomization[1] **aims to avoid systematic error** (BIAS) due to the imbalance in confounding factors between intervention and comparator groups in a clinical trial. While it would be possible to record multiple patient characteristics (such as age, sex, diabetes status) and then divide patients into approximately equal groups, this method can only **be applied once all participants** have been **recruited**. More importantly, it does not take unmeasured and unknown factors into account that might still affect the outcome of the trial. Moreover, if the treating physician or researcher can choose allocation, selection bias might compromise the study's results. **Randomization** solves these issues and has become the cornerstone of **modern clinical research**.

Proper randomization relies on computer-generated random numbers. The use of naturally occurring patterns – such as allocating patients dialyzing during the morning shift to intervention groups and those dialyzing during the afternoon shift to comparison groups – is not randomization. Although it may seem that patients fall into these natural groups randomly, there's no guarantee that confounding factors will spread evenly between such groups.

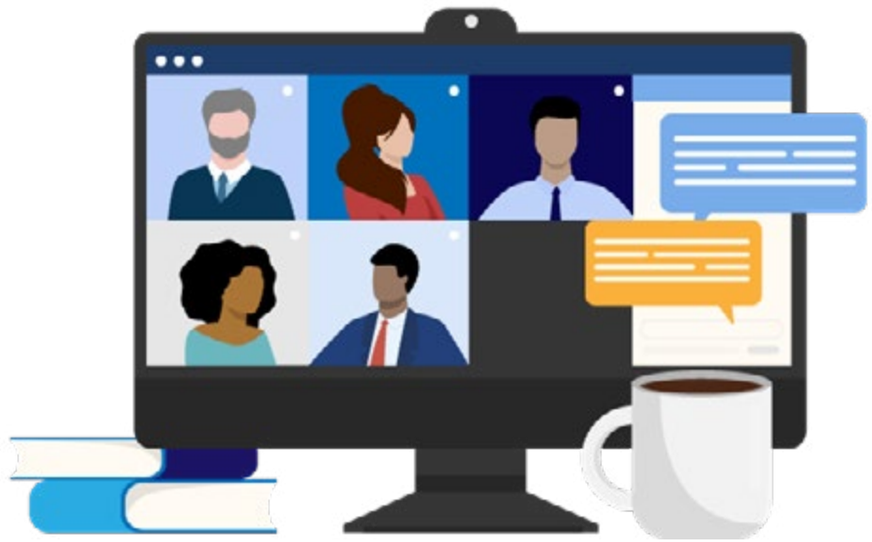
1.3. WHICH RANDOMIZATION METHOD SHOULD BE USED?

Dr. Pedro Augusto and Dr. Matheus Granado are both “Nephrorunners”, and combined the beauty of Melbourne with their favourite exercise.

Once back home, Dr. Pedro Augusto and Dr. Matheus Granado scheduled an online meeting with Prof. Smith. The main issue under **discussion** was **randomization methods**. They knew these could be divided into two categories: fixed allocation randomization and adaptive randomization. Most trials use fixed randomization, in which participants are allocated to intervention or comparator groups with a ‘fixed’ probability that doesn’t change throughout the study. In addition, fixed randomization can be further divided into simple, blocked, and stratified randomization. Adaptive randomization is more complex and permits the allocation probability to change as the study progresses.

1.3.1. Web meeting

As Prof. Smith was waiting for the Web meeting to start, he was **finishing up his grant proposal**. He knew the decision on the **randomization method** would be **critical** since this would impact two other trial sites, Brazil and Bolivia. Randomization plays an important role in the internal and external validity of a study. However, randomization comes at a price as it adds both complexity and bias to research. He knew the randomization method could become a weak link in the study because unwise decisions could result in the introduction of bias, which reviewers highly criticize.



Despite the difference in time zones, Dr. Pedro Augusto and Dr. Matheus Granado were on time for the meeting - they had no time to waste…

1.3.1.1. Fixed allocation randomization

A. Simple Randomization

The first to contribute to the discussion was **Mrs. Ana Luisa**, a Ph.D. candidate in Dr. Pedro Augusto's research group in Brazil. She had prepared herself for the meeting and was confident that the best choice was simple randomization.

"Simple randomization uses a random digit table (generated by a computer) or can even be done by flipping a coin. In this strategy, every patient has a 50% chance of receiving either an active or placebo treatment. Because each participant's allocation is completely independent, it is impossible to guess which group a participant will be allocated to before performing the randomization. This is an essential feature since it assures "allocation concealment." To prevent selection bias in patient recruitment, it is vital that the researcher or clinician enrolling the patient does not know (or cannot guess) what the patient's likely treatment allocation will be."

Dr. Pedro Augusto interrupted:

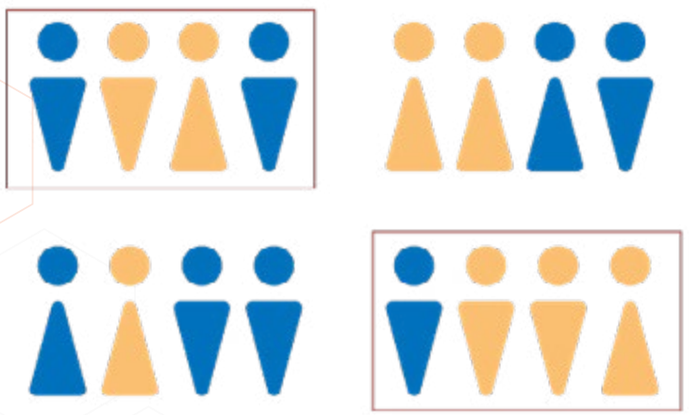
"We have to make sure we'll be able to **recruit enough patients**. When used in trials with small samples, simple randomization often results in imbalanced groups simply by chance." He went on, "Suppose now that you are randomizing a small group of 10 subjects (8 men and 2 women) into two groups of 5 subjects using a simple randomization method. It is possible that one of the groups will contain only men (instead of 4 men and 1 woman per group). If men respond better to the drug X340, then an imbalanced sample will bias the results."

B. Blocked randomization

The next to talk was **Dr. Matheus Granado**. As an expert in evidence-based medicine, he is a leader in the critical analysis of studies in his country.

He decided to move on to discuss “blocked randomization”:

“In this method, the principal investigator defines **block sizes** so that randomization will occur in blocks of a fixed number. This method has the potential advantage of decreasing the likelihood that at the end of the study there will be differences in the number of subjects across groups of treatment (imbalances).”



Mrs. Julia Aguiar, Dr. Matheus Granado’s MSc Fellow, continued in the same line:

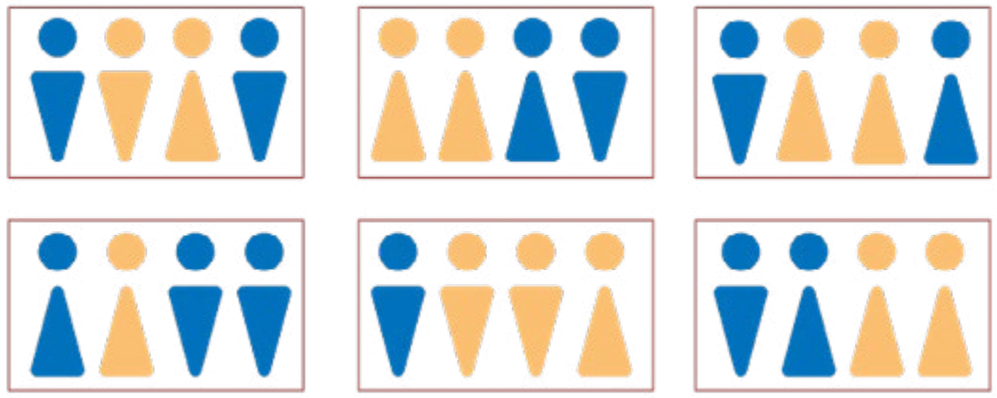
“However, a potential disadvantage to this method is that investigators might guess the treatment allocation at the end of the block.

This could result in selection bias since a researcher might consider not randomizing a patient if he’s certain the following patient will be allocated to a specific arm of the study.”

C. Stratified randomization

Dr. Pedro Augusto was listening attentively to the discussion. It was late at night in Brazil, and he had to take care not to wake his three children while he talked. Slowly, and with a Brazilian accent, he mentioned the stratified randomization method:

“In this method, patients are randomized in strata of covariates considered to play a role in the outcome of the study (e.g., age, CKD stage). This method **reduces the risk of chance imbalance in important covariates** because a patient will only be randomized into the active or the placebo groups



after being assigned to each stratum. As the process is more complex, it can lead to bias if used with simple randomization techniques. When used with block randomization it can also generate the problem of un-blinding at the end of blocks, as already mentioned. Another point to consider is that since the participant cohort is further divided into strata, the issue of imbalances for small sample sizes can be hard to overcome."

1.3.1.2. Adaptive randomization

Being the most experienced in the group, Prof. Smith introduced a less commonly used randomization method, whose additional complexity makes it difficult to implement.

"When we use a randomization system that varies depending on the characteristics of **participants already randomized**, we call it adaptive randomization. In this scenario," he said, "there are two categories to be explored."

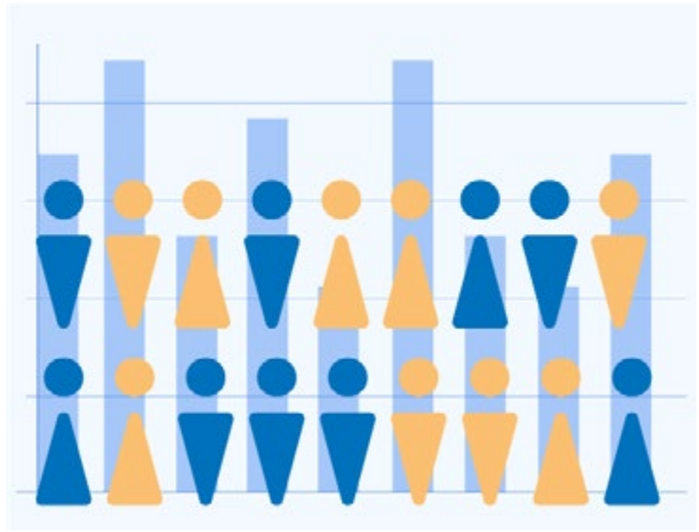
A. Minimization Technique: Randomizing Patients According to an Algorithm

"The minimization technique applies an algorithm to change the likelihood that a given patient will receive active or placebo treatment according to

pre-specified baseline characteristics. Essentially, it's a more complex form of stratified randomization that continuously adjusts probabilities to maintain balance throughout the recruitment period."

B. Adaptive Randomization According to the Response

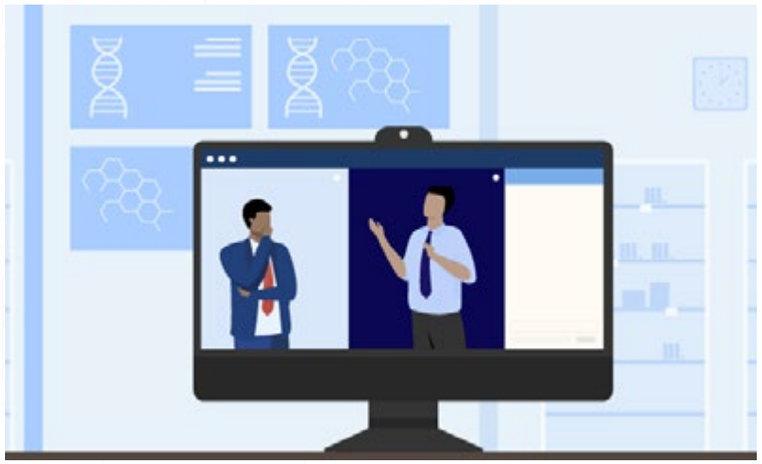
"In this method, every new patient is randomized according to the response of the previous patient.



For example, if the first patient is randomized to the active treatment and responds, the subsequent patient will also be randomized to the active treatment until no response is achieved. When this happens, the next patient will be switched to the control treatment."

"But be aware," Prof. Smith added, "while minimization technique and response adaptive randomization are interesting methods, they are complex to implement and require sophisticated statistical support."

With this in mind, Dr. Pedro Augusto and Dr. Matheus Granado quickly reviewed their notes. New perspectives on research methods had opened up to them, and they would need more time before making a **final decision on which randomization method to use**.



Don't miss the next chapter in June 2021!

1 https://www.theisn.org/in-action/research/clinical-trials-isn-act/isn-act-toolkit/study-stage-1-design-and-development/randomization/

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