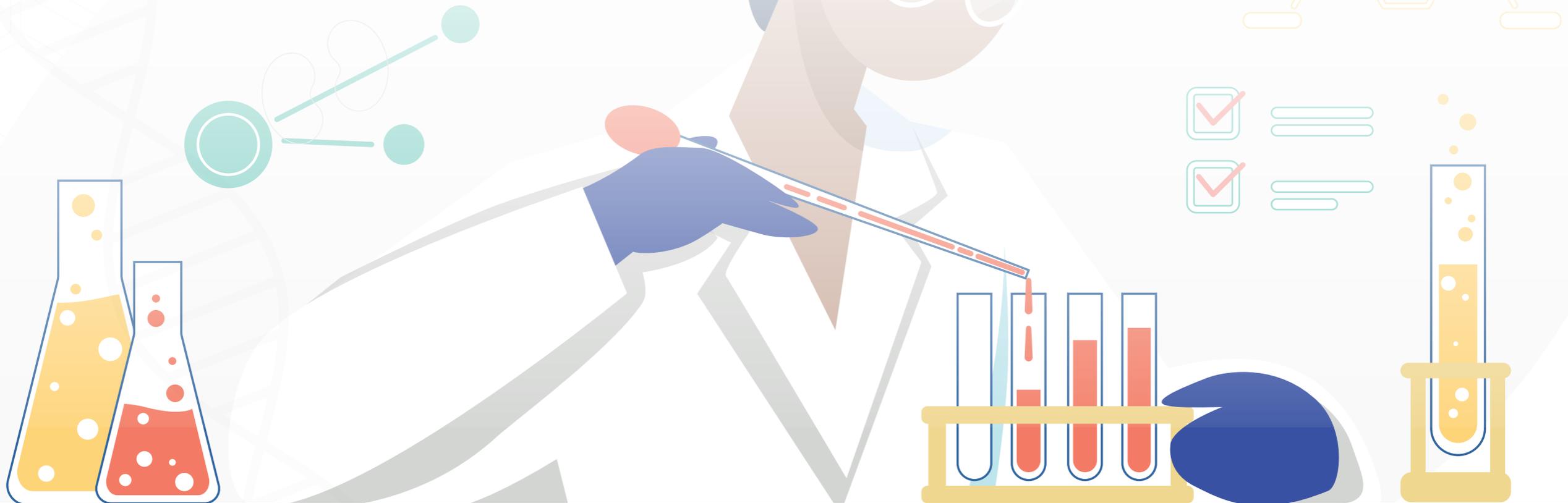


# CLINICAL TRIALS TOOLKIT

## Chapter 2 - Trial Designs

June 2021



# 2. CASE STUDY – TRIAL DESIGNS

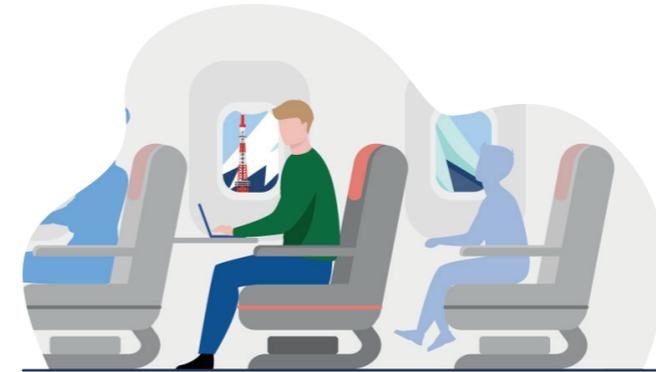
By M.D. Ph.D. Augusto Cesar Soares dos Santos Junior (Brazil), M.D. Brendan Smyth (Australia), M.D. Sonia Sharma (India) and M.D. Rahul Chanchlani (Canada).

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.

## 2.1 INTRODUCTION



**Dr. Sebastien**, a junior nephrologist based in Leuven, Belgium, had received a travel grant to join a meeting in Tokyo, Japan, organized by the International Society of Nephrology (ISN).



The conference would gather a group of leading nephrologists to discuss one of Dr. Sebastien’s preferred themes: “Kidney and Inherited Disorders.” An enthusiast of new therapies for autosomal dominant polycystic kidney disease (ADPKD), he knew this theme would be central to the discussions. ADPKD is the most common inherited cystic kidney disease and one of the most important causes of kidney failure requiring dialysis or kidney transplantation worldwide.

On the flight, he decided to double-check the scientific program to make sure he wouldn’t miss any presentations on new approaches to ADPKD. He was planning to start a research study on this topic and was keen to exchange ideas on different options for randomized study designs.

## 2.2 STUDY DESIGN<sup>1</sup>

The design of a clinical trial describes a sequence and structure of activities aiming to reveal a cause-and-effect relationship as defined in the research question. All trials begin with a single group of participants (the COHORT) who are selected to represent a defined disease population. This cohort is then divided into two or more groups subjected to an intervention and comparator. The groups are then observed for the outcome of interest. The difference in outcome between the groups is then calculated to determine the effect of the intervention.

## 2.3 THE ISN MEETING

Dr. Sebastien took a front-row seat at the opening ceremony. The meeting was set up so that all participants were in one large room to facilitate discussion and collaboration. Cocktails were served at the end of the day, and Dr. Sebastien was looking forward to meeting **Dr. Rosana**, one of the most prominent scientists at the conference. He knew the current results of non-controlled studies on the effects of new ADPKD treatment needed further testing in more elaborate, randomized controlled trials. He wanted to discuss the design options with her, notably the idea of a parallel clinical trial. He made a beeline for Dr. Rosana and started talking to her about his planned trial method.



### 2.3.1 Parallel-group Trial<sup>2</sup>

This is the most common trial design. Participants are randomized to different groups (sometimes referred to as ‘arms’) which receive the intervention (often referred to as treatment or experimental arm) or comparator (which may be control, placebo, or active comparator). The groups are then followed for a specified time (the study duration), and the outcome is measured. Parallel-group trials usually have two groups, but three or more groups are sometimes used (e.g., In a three-group trial, the intervention can be simultaneously compared against the standard treatment and placebo). Adding more groups means that more participants have to be recruited to maintain power.

Depending on the statistical methods, parallel-group trials can test for superiority (that the intervention is better than the comparator), non-inferiority (that the intervention is not worse than the comparator), or equivalence.

So key steps involved here include assessing participants’ eligibility to recruitment and randomization to either treatment arm or experimental arm.

Based in Milano, Italy, Dr. Rosana was well known for her dedication to clinical research, her strong work ethic, and her ability to cooperate with many different research



teams. She was impressed by Dr. Sebastien's enthusiasm, so although she was tired from the long trip, she provided Dr. Sebastien with an outline of a different randomized clinical trial design, one he hadn't heard of before; cross-over trials.

### 2.3.2 Cross-over Trial<sup>3</sup>

In a cross-over trial, participants receive both the intervention and the comparator but at different times. So a participant who starts receiving the intervention will change to the comparator in the second half of the study and vice-versa. Cross-over studies are suited to study the effects of interventions on short-term changes in reversible outcomes (e.g., blood pressure).

Because each participant acts in both the intervention and the comparator groups, the variation within the cohort is reduced. This allows cross-over studies to be smaller than equivalent parallel-group trials while maintaining study power.

On the other hand, cross-over trials must be careful to avoid bias caused by switching treatments. It is necessary that the underlying disease state or condition is chronic and remains stable throughout the study period and that the effect of the intervention does not carry over into the comparator period (or vice-versa). Most cross-over studies use a wash-out period to avoid this latter problem. In addition, it's critical that the order of treatment does not interfere with study results (e.g., if the intervention cures or permanently changes the disease state).

Dr. Sebastien couldn't believe his luck at being able to discuss study designs with a true translational scientist. Much of Dr. Rosana's research was conducted using animal models, but she was also an expert at translating her findings into clinical outcomes in humans. After this initial encounter, they decided to discuss design options further the following day.



Dr. Sebastien then headed back to his hotel, unaware that more unexpected good fortune lay ahead. His travel grant meant sharing a room with a fellow young nephrologist – **Dr. Aarav**, a travel grantee from Bangalore, India. Dr. Aarav is committed to helping his community, especially those from disadvantaged populations, and therefore has a special interest in studying social and economic determinants as factors in the progression of chronic kidney diseases.

It wasn't long before Dr. Sebastien was describing his earlier conversation with Dr. Rosana to his roommate, and he soon discovered that Dr. Aarav had already



participated in the design of a “factorial trial.” So now Dr. Sebastien had another new perspective – he had never imagined he would learn so much on his first day at the conference.

### 2.3.3 Factorial Trial<sup>4</sup>

A Factorial trial is a parallel trial in which two sets of intervention and comparator are tested simultaneously. They are also known as 2 by 2 studies as they divide patients into four groups which can be represented in a 2 x 2 table. They increase trial efficiency by using one cohort to test two different trial questions. In addition, they can also test if the combination of interventions has a different effect on either group on their own. Note that despite having two interventions, there will still only be one outcome. The main disadvantage of this type of trial is the large sample size required to achieve enough power. Another issue is that its design adds complexity to the implementation and analysis of the results.

The next day, Dr. Sebastien was still going through the pros and cons of each clinical trial design. He invited Dr. Aarav to join him and share his thoughts on factorial trials with Dr. Rosana. They decided seek her out at the conference hall before the first session began.

Dr. Rosana had received support from the ISN as a young nephrologist and considered it a priority to help future

generations of nephrologists, so she was happy to talk to them both, introducing them to a type of clinical trial they were not familiar with – cluster trials:



### 2.3.4 Cluster Trial<sup>5</sup>

Cluster trials differ from other types in that groups of participants, not individual participants, are allocated to different treatments. They are most useful when the trial intervention is a health care practice rather than an individual treatment. Examples include the use of antimicrobial detergents in hospital cleaning products. In this example, all patients at the hospital are affected and cannot be effectively split into groups. Cluster trials avoid this problem by involving multiple groups of patients (e.g., hospital, clinic, or dialysis shift) and allocating whole groups (i.e., clusters) to the intervention or comparator. The outcomes on individual patients are then compared using statistical methods that account for the fact that patients were grouped together in clusters.

After this short explanation, Dr. Rosana left to present the opening lecture.



Dr. Sebastien decided to stay for a couple more minutes to organize his ideas. He had a strong feeling that the conference in Tokyo would prove to be one of the most valuable experiences in his professional career.

**Don't miss the next chapter in October 2021!**

#### Notes

- 1 <https://www.theisn.org/in-action/research/clinical-trials-isn-act/isn-act-toolkit/study-stage-1-design-and-development/trial-design/>
- 2 <https://www.theisn.org/in-action/research/clinical-trials-isn-act/isn-act-toolkit/study-stage-1-design-and-development/trial-design/#parallel-group>
- 3 <https://www.theisn.org/in-action/research/clinical-trials-isn-act/isn-act-toolkit/study-stage-1-design-and-development/trial-design/#cross-over>
- 4 <https://www.theisn.org/in-action/research/clinical-trials-isn-act/isn-act-toolkit/study-stage-1-design-and-development/trial-design/#factorial>
- 5 <https://www.theisn.org/in-action/research/clinical-trials-isn-act/isn-act-toolkit/study-stage-1-design-and-development/trial-design/#cluster-trials>

This publication is for educational purposes only. The safety and scientific validity of a study is the responsibility of the study sponsor and investigators.

© International Society of Nephrology, 2021

No part of this publication may be reproduced, translated, or transmitted in any form or by any means without the prior written permission of the International Society of Nephrology.

Design and layout: International Society of Nephrology

Editing and proofreading: International Society of Nephrology