



Chapter 05 / Capítulo 05

Evidence-based biomedicine: methodology for research, standardization, and scientific procedural aspects (English Edition)

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Experimental Studies. Randomized Clinical Trial / Estudios Experimentales. Ensayo Clínico Aleatorio

In contrast to observational studies described in previous chapters, experimental studies can determine causal relationships between variables. This is possible because in these studies, the research team has direct control over the intervention. While in observational studies the researcher measures the disease or cause-effect relationship without intervening, in experimental studies, they can actively manipulate the cause to reproduce and study the desired cause-effect relationship. These studies are used to evaluate the effectiveness of therapeutic, preventive, and rehabilitative interventions, as well as planning and programming activities in the health sector. Experimental studies are divided into two main categories: clinical trials and community trial.

5.1. Clinical trial

A clinical trial (CT) is a type of experiment conducted on humans that involves comparing two or more groups of individuals who are as similar as possible in terms of characteristics. These groups receive different treatments or interventions to assess which is more or less beneficial. According to Royal Decree 223/2004, of February 6, which regulates clinical trials with drugs in Spain, they are defined as research conducted on people to determine or verify clinical and pharmacological effects, among other pharmacodynamic effects, identifying adverse reactions, and to study the absorption, distribution, metabolism, and excretion of one or more investigational drugs, all to establish their safety and efficacy.

5.1.1. Types of clinical trials

Depending on the objectives, the following phases are addressed for the structuring and development of new drugs:

- **Phase I Clinical Trial:** this marks the start of human research into a new drug. It is typically conducted with a small number of healthy volunteers and provides initial data on the drug's dosage and side effects.
- **Phase II Clinical Trial:** this is conducted in patients with the disease the drug seeks to cure or alleviate. The main focus is on evaluating the product's efficacy. The objective is to determine the relationship between dose and response, identify variables to measure efficacy, and expand on the safety information obtained in Phase I. These trials must be controlled, and participants must be assigned randomly.
- **Phase III Clinical Trial:** the final phase of the therapeutic evaluation of the treatment. It focuses on evaluating the efficacy and safety of the experimental treatment under conditions that simulate normal use, while accounting for existing therapeutic alternatives for the indication under study. It is conducted with a larger and more representative sample than in Phase II. These clinical trials are controlled and randomized. After completing these three phases, authorization to market the drug or therapeutic device can be requested.
- **Phase IV Clinical Trial:** this is conducted once the drug has been marketed and is designed to evaluate the long-term safety and efficacy of the drug, as well as to explore new indications for use.

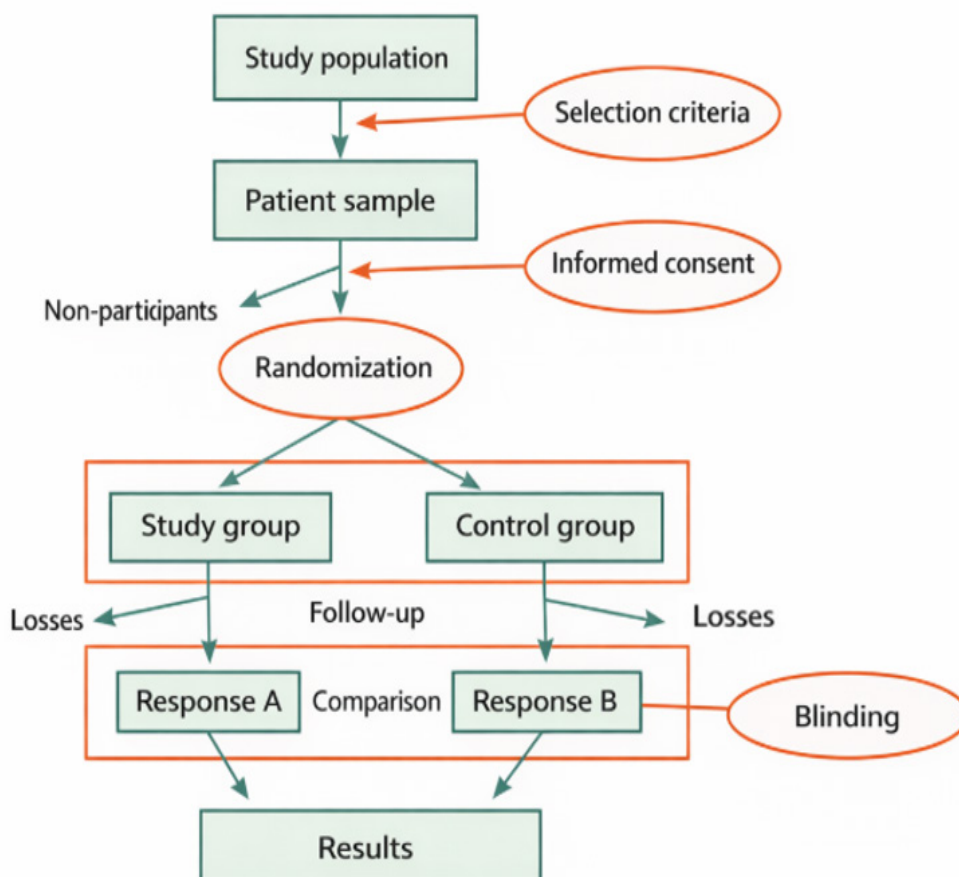


Figure 5.1. General outline of a parallel group controlled clinical trial

According to the methodological approach of the designs

- **Controlled Clinical Trial:** in this type of trial, a “control group” is used that does not receive the intervention under study, allowing the results obtained to be compared. The internal validity of a controlled clinical trial depends on the similarity between the groups in all aspects except the intervention under analysis. There are two types of controlled clinical trials:
 - **Controlled Clinical Trial with Parallel Groups:** in this design, one or more groups of subjects receive the experimental treatment, while another group receives a control treatment or placebo.
 - **Controlled Clinical Trial with Crossover Groups:** in this design, treatments (experimental and control) are administered to each individual in randomly assigned successive periods. This allows each participant to act as their own control.
 - **Uncontrolled Trial (Before-After Studies):** this type of study does not include a control group. The response to the intervention is evaluated in the same group of subjects, comparing the results before and after the intervention..

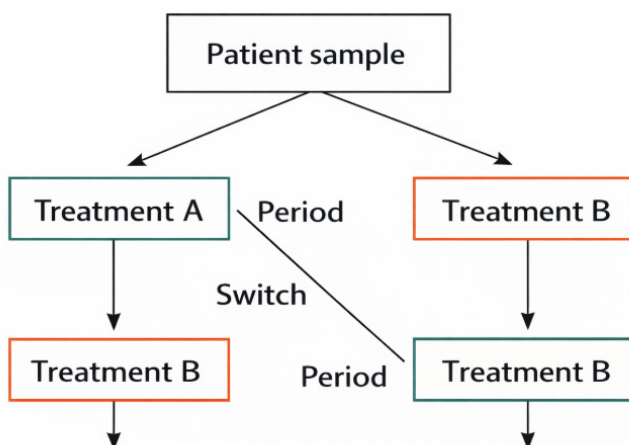


Figure 5.2. General outline of a crossover clinical trial

5.1.2. Methodological basis for clinical trial designs

The design of a clinical trial must include the following fundamental elements:

1. Ethical considerations and justification for the clinical trial.
2. Clear definition of the study objectives.
3. Determination of the target population for the study.
4. Selection of patients and obtaining their informed consent.
5. Implementation of the randomization process and application of masking techniques.
6. Detailed description of the intervention to be performed.
7. Rigorous follow-up of study participants.
8. Strategy for data analysis and comparison of results between the intervention and control groups to determine the impact of the intervention.

Consequently, some basic aspects of clinical case designs are established.

Setting objectives:

When formulating the objectives of a Clinical Trial (CT), it is essential to precisely define:

1. The characteristics of the patients to be included (study population).
2. The intervention to be studied (intervention or study factor).
3. The interventions with which the comparison will be made.
4. The variables that will be used to evaluate the effectiveness of the study (response variable).

For example, a study might ask: “Is group health education effective in improving control in diabetic patients?” A specific objective of the study could be: “To evaluate the effectiveness of a group community intervention, including health education and physical exercise, compared to routine follow-up in the doctor’s office, to improve metabolic control (reduction of glycated hemoglobin) in patients with type 2 diabetes, controlled and without complications, aged 40 to 70, in a basic health zone in Cartagena.”

This objective can be broken down into:

1. Study population: patients aged 40 to 70 years with type 2 diabetes who are controlled and without complications.
2. Intervention or study factor: group diabetes education and monitored aerobic physical exercise.
3. Intervention with which it is compared: routine follow-up in primary care, according to the diabetes program.
4. Response variable: reduction in glycated hemoglobin.
5. If the objectives of the study are not clearly defined, its validity may be compromised.

Likewise, when defining the study sample, it should be noted that the target population is the population to which the study's results are intended to be applied. Still, the study is carried out in a specific population that meets certain selection criteria, called the study or experimental population. From this study population, a sample of subjects who will participate in the trial is obtained.

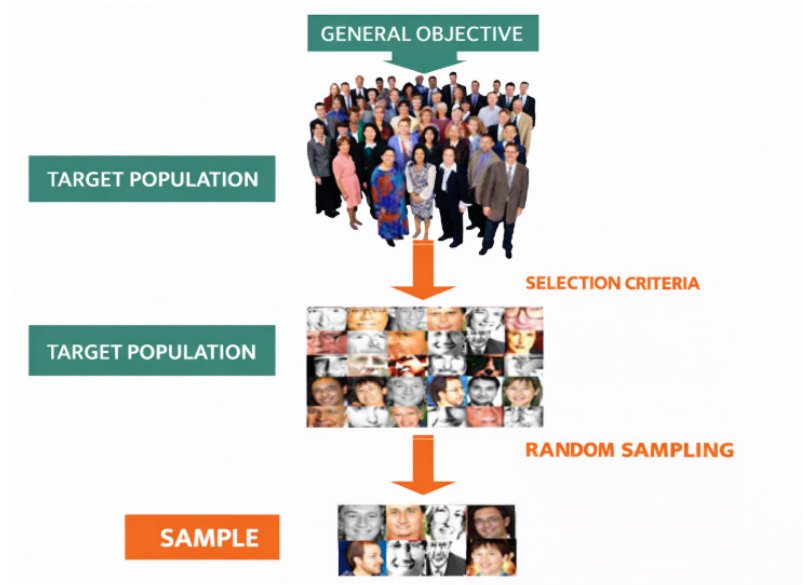


Figure 5.3. Types of population

5.1.3. Random assignment

Randomization is a systematic, reproducible procedure for assigning clinical trial participants to different treatment groups. This technique ensures that the groups are comparable by generating a balanced distribution of both known and unknown variables.

The random assignment of participants to groups is carried out after they have been admitted to the trial, i.e., once it has been verified, through various tests (such as questionnaires, examinations, and analyses), that they meet the inclusion criteria and have given their informed consent. In this way, the decision to include a patient in the study is not influenced by prior knowledge of the treatment they will receive.

5.1.4. Masking techniques

The expectations of both researchers and patients can influence the evaluation of the results observed in a clinical study. To avoid this bias, various masking techniques are used, including:

1. Single-blind: In this approach, study participants are unaware of which treatment group they have been assigned to.
2. Double-blind: Both participants and researchers administering the treatment are unaware of the type of treatment being administered, ensuring a higher level of impartiality in the evaluation.
3. Triple-blind: In this technique, neither the participants, the researchers, nor the person responsible for analyzing the final results of the study know what type of intervention has been carried out in each group.

When these masking techniques are not possible, masked response assessment or blinded evaluator assessment is used. This means that the person responsible for measure the response variable, does not know which group each of the subjects belongs to, which helps to minimize any bias in the evaluation of the results.

5.1.5. Follow-up of clinical trial participants

The comparability achieved through random assignment of participants must be maintained throughout the study. Therefore, it is essential that the scheduling of reviews and scans be consistent for all participants.

Follow-up of participants should be appropriate to the trial objective and sufficiently long to allow the expected response to occur. However, it is important to note that as follow-up time increases, the likelihood of participants being lost to follow-up or withdrawing from the study also increases.

The term “post-randomization losses” refers to patients who drop out or are withdrawn from the study after being assigned to a treatment group. All such losses must be documented and included in the clinical trial report to assess their potential impact on the study results.

5.1.6. Analysis strategies

The analysis strategy in a clinical trial is similar to that of other studies comparing multiple interventions, as discussed in previous sections. However, in clinical trials, situations may arise that require deciding whether to exclude some observations or participants from the analysis, and this decision may influence the study’s conclusions.

There are several possibilities for analysis in a clinical trial:

1. Exclude losses and deviations from the protocol from the final analysis and consider only those participants in each group who followed and completed the trial protocol. This strategy is known as “valid case analysis” or “per-protocol analysis.”
2. Analyze participants in the treatment group to which they were assigned, even if they underwent a different intervention than the one assigned. This is called “treatment analysis.”
3. Analyze participants in the group to which they were assigned, regardless of whether they complied with the assigned intervention or received a different treatment. This strategy is called “intention-to-treat” (ITT) analysis.

The last strategy, the intention-to-treat (ITT) analysis, is considered the most appropriate in a clinical trial, as it maintains comparability between groups and is the most conservative option. In other words, it is the strategy that makes it most difficult to achieve positive results in favor of the new intervention.

It is important to note that participant losses that occur before random assignment do not bias the comparison of data and therefore do not affect the internal validity of the study, but they may influence the generalization of the results (external validity).

5.2. Community trial

Community trials, also known as community-level trials, refer to studies in which an intervention is implemented in an entire community, while another community is used as a control group. These trials fall under the category of experimental studies, as they are designed to test a hypothesis and are structured around an experimental population and a control population. It is important to note that these designs are called “quasi-experimental” because they involve the manipulation of variables, but randomization is not used.

When experimental studies are conducted with an appropriate design, sufficient sample size, careful randomization, controlled intervention, and rigorous follow-up, they can provide solid evidence that allows us to conclude the presence of causal relationships between variables.