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Experimental analytical trials. The clinical trial

Estudios analíticos experimentales. El ensayo clínico

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Abstract

As we have previously discussed in a previous article, analytical studies are those in which there are comparison groups that allow us to study the association of study factors with final events or outcomes, such as smoking and the development of AAA.

In this article, we will analyze the experimental analytical studies or, simply, experimental ones, because we can consider experimental studies to be analytical by nature, given the presence of 2 comparison groups, for example, the survival rates of 2 different types of treatment.

Keywords: Scientific methodology. Experimental analytical studies. Clinical trial.

Resumen

Como hemos comentado anteriormente en un artículo previos, los estudios analíticos son aquellos en los que hay grupos de comparación que nos permiten el estudio de asociación de factores de estudio con eventos finales o resultados, como por ejemplo el tabaquismo y el desarrollo de AAA.

En este artículo trataremos los estudios analíticos experimentales o, simplemente experimentales ya que podemos considerar que siempre los experimentales son analíticos al existir 2 grupos de comparación, por ejemplo, supervivencia de 2 tipos diferentes de tratamiento

Palabras clave: Metodología científica. Estudios analíticos experimentales. Ensayo clínico

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EXPERIMENTAL TRIALS

As mentioned in previous articles (1), analytical trials are those with comparison groups that allow us to study the association of study factors with final events or outcomes, such as smoking and the development of AAA.

fWe mentioned (1) that analytical trials can be categorized into observational and experimental trials. The former have been previously discussed (2). We will now be discussing experimental analytical trials, or simply called experimental trials since we can always consider experimental trials to be analytical since they involve 2 different comparison groups, such as the survival of 2 different types of treatment.

An experimental design is a study in which the researcher assigns the study factor to a certain group of patients. The researcher, then, decides which subjects will receive drug A or drug B. This allocation is randomized (determined by chance), and significantly reduces the likelihood of biases improving the internal validity of our study. Randomization guarantees that subjects will receive one treatment or the other randomly. However, if randomization works correctly, we will have the advantage that the comparison groups will be very similar in terms of variables that could impact the outcomes. Therefore, any differences we may find between the groups can be attributed to the intervention because all other variables will be "equated" among the different groups.

Experimental trials can, therefore, be categorized into 2 main branches based on whether randomization is used or not, as illustrated in figure 1.

To keep this explanation concise, we will focus on developing the experimental trial that is most frequently found in the scientific medical literature: the clinical trial.

THE CLINICAL TRIAL

We speak of clinical trial (CT) to refer to prospective and experimental trials in which, once the sample has been selected, it is randomly categorized into 2 groups with comparable prognoses that

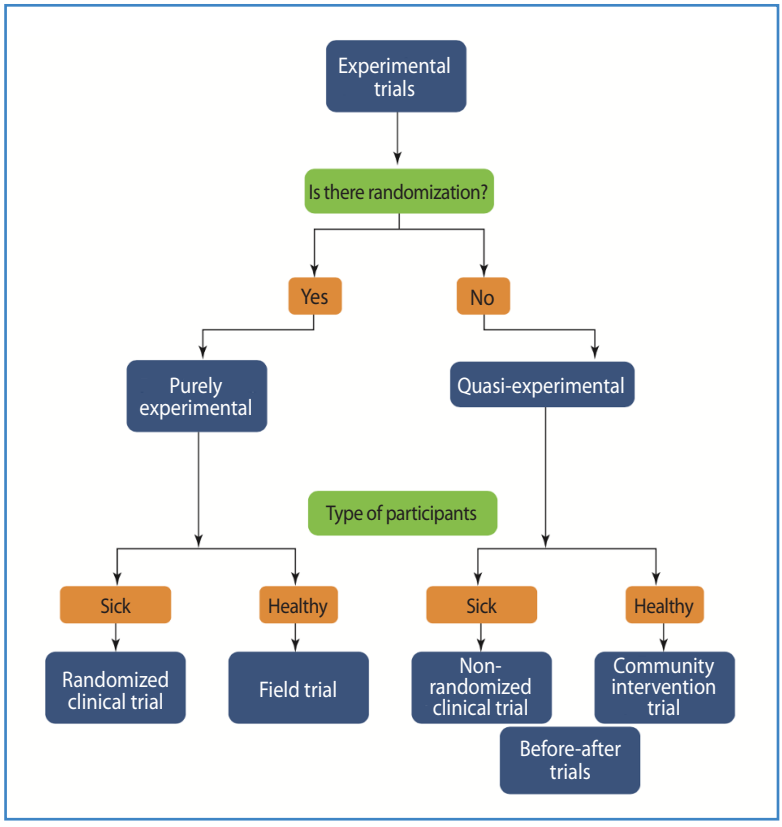

Figure 1. *Classification of experimental designs.*

ideally only differ in the therapeutic intervention they will receive.

Moving away from theoretical arguments, are clinical trials a methodology on the rise? The Spanish Agency of Medicines and Medical Devices (AEMPS) states that, in Spain, clinical research regarding these designs, is considerably good (Fig. 2). Unfortunately, the part of these studies that is exclusive to our medical specialty is scarce. Cardiology is the specialty that engulfs most studies within the cardiovascular category.

Stages involved in a clinical trial

Many of the stages involved the development of a clinical trial are common to other designs. Additionally, we can see that these are logical and evident steps within the epidemiological method. To guarantee an organized explanation, we will stick to the stages already outlined by Hulley et al. back in 1988:

- *Selection of the study cohort:* By formulating inclusion criteria, the clinical and sociodemographic characteristics of the patients who will eventually receive the drug are established. Exclusion criteria are used to reject patients with inclusion criteria but with contraindications, conditions that could affect the outcome variable, or any other characteristics that could complicate their study.
  In this stage, the sample size needs to be determined, and it should be large enough to obtain a 95 %CI regarding efficacy with clinically relevant limits.
- *Measurement of baseline variables:* This involves determining a series of variables in subjects who meet the inclusion criteria and have agreed to participate in the study (informed consent). The aim is to provide a series of data to later verify that randomization has been effective and eventually conduct the analysis.
  - *Randomization:* Randomization involves randomly allocating patients in the sample

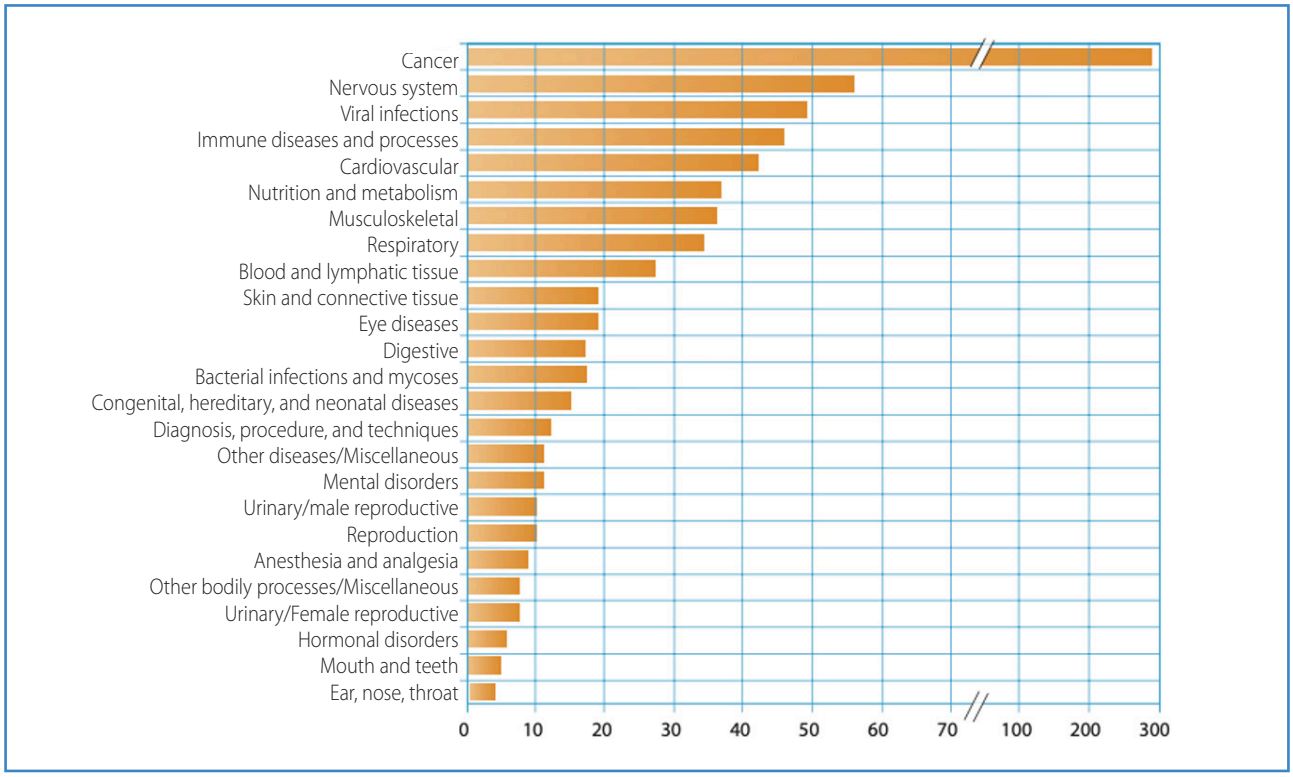

Figure 2. *Distribution of CTs by medical specialties (2015).*

to the 2 intervention groups, without any influence from any factor. If the sample size is large enough, a homogeneous distribution of predictor variables is achieved in both groups. Randomization can be done in 3 different ways:

- *Simple randomization:* Each patient has the same chances of being randomized to either treatment group. This method poses a risk of numerical inequality between the groups. Tossing a coin would be the best example to explain this. Each patient would have a 50 % chance of receiving either treatment. However, uneven group sizes can be problematic in studies with a small sample size.
- *Block randomization:* Randomization is done in blocks in such a way that in each block, half of the patients receive the experimental treatment and the other half the control treatment. Each block contains the same number of subjects on either treatment, which guarantees equal group sizes.
- *Stratified randomization:* Patients are categorized into homogeneous groups (strata) with respect to a prognostic variable of interest, and they are randomized to 1 of the 2 intervention groups. For example, when comparing the survival of EVAR and OR in the management of AAA, stratifying by age would be appropriate, as age *per se* could justify different survival rates between the treatment groups.

– *Implementation of the intervention:* It is important to make sure that both researchers and caregivers do not treat the 2 intervention groups differently. To avoid this, called cointervention bias, and to prevent the measurement of the outcome variable from being biased for the same reason, masking is used. Three types of masking are often used:
  - Single-blind: The patient is unaware of the treatment group to which he/she is randomized.
  - Double-blind: Both the patient and the health care evaluator of the outcome variable are unaware of the treatment group.
  - Triple-blind: In addition to the above, the data analyst is unaware of the type of treatment for each group.
– *Data analysis:* Two fundamental aspects should be considered. First, losses of subjects included in the CT that occur before randomization will affect the generalizability of the results, while post-randomization losses can affect internal validity. Also, we are not dealing with a novel methodology: the statistical analysis of CTs is very similar to that of cohort studies (2). Nonetheless, the use of non-parametric methods is more common, and the use of survival analysis (3) is important to determine when the outcome variable occurs.

Stages involved when conducting a TC

Considering the objectives pursued in drug development, 4 phases can be seen here, as illustrated in table I.

– *Phase I trial:* This is the first time a drug is administered to humans. It is often conducted among healthy volunteers (20 to 80 subjects) and without a control group. These are often open-label, non-randomized, and often non-comparative clinical trials. The main objective is to evaluate toxicity and determine the maximum tolerated dose. They are limited to the experimental setting, or their pharmacokinetic and pharmacodynamic effects. For example, bioequivalence studies with generics fall into this phase.
– *Phase II trial:* The primary objective is to provide information on the dose-response relationship, providing preliminary information regarding efficacy. It is conducted in patients with the disease of interest (n = 100 to 200). It does not necessarily have to be comparative. Typically, this type of clinical trial is controlled and uses treatment randomization.
– *Phase III trial:* This is the prototypical CT. It is often comparative with standard therapy, or placebo. It is the most extensive and rigorous clinical research of a medical therapy, and serves to establish the efficacy profile of a new

drug, and the existence of common adverse events. Phase III trials are often conducted with a larger group of patients selected with less strict inclusion/exclusion criteria, often involving patients on multiple drugs and allow for extrapolation of results to the broader population (external validity).

– *Phase IV trial:* This involves conducting a clinical trial with drugs or procedures for which there is already an approved indication. This involves conducting CTs with patients from the routine clinical practice, which allows for drawing conclusions on adverse events, efficacy, and even new indications.

Types of clinical trials

Although we have seen the overall characteristics of clinical trials, some of them have unique features. We list them in table II.

– *Protocol-defined CT:* It includes only those patients who have met the protocol requirements, or completed the study. The setback here is that the participants who complete the studies are often those who respond well to treatment. If we only analyze these subjects, we may provide a biased picture that favors treatment with more dropouts.

– *Intention-to-treat CT:* The analysis includes all patients who were selected and allocated to the group, even if they have not completed the study or changed groups. This design approximates the routine clinical practice, underestimates the differences between treatment arms, and simulates clinical reality.

– *Parallel-group CT:* The control group receives treatment at the same time as the experimental group to control for prognostic factors effect over time (that may change). Data analysis involves comparing the difference in the outcome variable between both groups with the expected variability within each group due to chance. It is very suitable for acute diseases.

– *Crossover CT:* In this design, the same patient receives both treatments being compared in 2 different moments in such a way that the patient serves as his/her own control, allowing

Table I. Phases of the clinical trial

Main characteristic		Objective	Sample
Phase I	Initial steps in drug research in humans	Initial estimation of tolerance, safety, pharmacokinetics, and pharmacodynamics No assessment of efficacy	Usually, only a few healthy volunteers (n = 20-80) do not typically have a control group or masking
Phase II*	Therapeutic trial, yet only exploratory	Preliminary information on efficacy, dose-response pattern, tolerance, and expansion of safety data from Phase I	Small trials (n = 100-200) in patients with the disease of interest Preferably with a control group
Phase III	The most common one in medical publications Aimed at achieving drug approval or marketing	Demonstrate therapeutic effect (efficacy) Evaluate the safety profile of the new drug compared to other alternatives available	Larger sample of patients with a specific single disease Controlled and randomized
Phase IV	Post-marketing and long-term surveillance	Evaluate safety and efficacy profile, new indications, side effects, long-term morbidity, and mortality	Preferably controlled and randomized

Table II. Types of clinical trials

Pragmatic	Heterogeneous sample, external validity
Explanatory	Homogeneous sample, internal validity
Cross-over	Each group takes both drugs with a washout period
Parallel	Each group takes a single drug
Intention-to-treat	All included subjects are analyzed
Per-protocol	Only those who complete the study are analyzed
Predetermined size	Known sample size beforehand
Sequential	Progressive inclusion of patients in the study
Superiority	Demonstrate that one drug is better than the other
Non-inferiority	Assuming similar efficacy, the new drug has other advantages
Masked	Use of blinding techniques to avoid biases
Open	Not blinded

for a smaller sample size compared to the classical design by reducing variability. The disadvantages are:

- Assuming the absence of residual effects when observing the effect of one treatment (carryover). There must be a long enough washout period to make sure that the residual effects of the first allocated treatment do not remain.
- The sequence with which different treatments are administered may be associated with different responses (period effect).
- This design is not possible when the new therapy is surgical, or the first treatment aims to cure the disease definitively (eg, acute diseases).
- It is difficult to adjudicate late side effects.
- Statistical analysis is more complex than for parallel groups and requires the use of paired methods, or repeated measures.

– *Factorial CT:* In this design, 2 different treatments are simultaneously evaluated in the same sample of participants, with subjects being randomized to 1 of 4 possible groups: A, B, A + B, and placebo. In factorial trials, the placebos used must externally resemble the active treatment allocated in each sequence. This is the reason why we talk about "placebo A" and "placebo B" for the 2 treatments, A and B, respectively. The factorial design is often used when studying the efficacy of combined therapies. In this case, the drugs used may have different effects when combined, and in the end, it may be of interest to separately compare the 3 groups with some active treatment (Fig. 3).

– *Non-inferiority CT:* CTs are often conducted to demonstrate the superiority of one drug over the other. However, it can be useful to prove that 2 drugs are, at least, equally effective, allowing for the use of the cheaper one. That is, it matters that it is not inferior in such a way that if it is equal or superior, the experimental drug is considered "not inferior" compared to the control group. Non-inferiority CT aim to demonstrate that the new therapy is the same or, if worse than the standard treatment, the difference between them would be very small and smaller than delta.

As mentioned earlier, therapeutic equivalence is defined based on non-inferiority trials. In these trials, 2 aspects should be considered (Fig. 4):

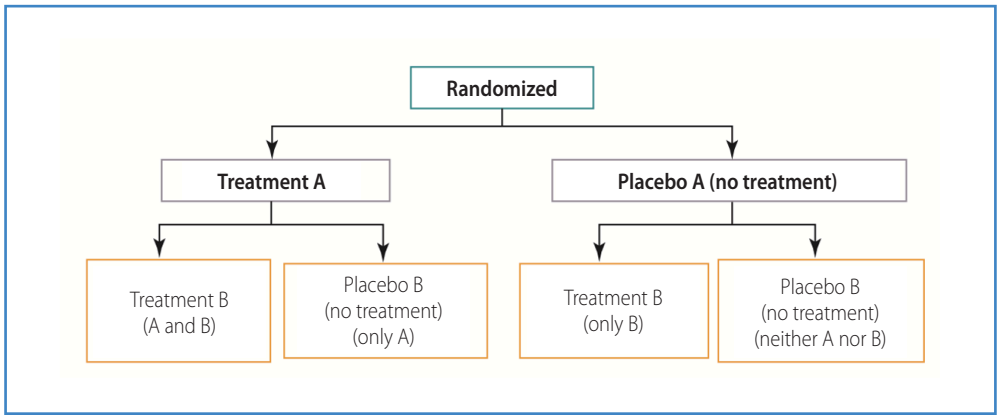

Figure 3. *Factorial design.*

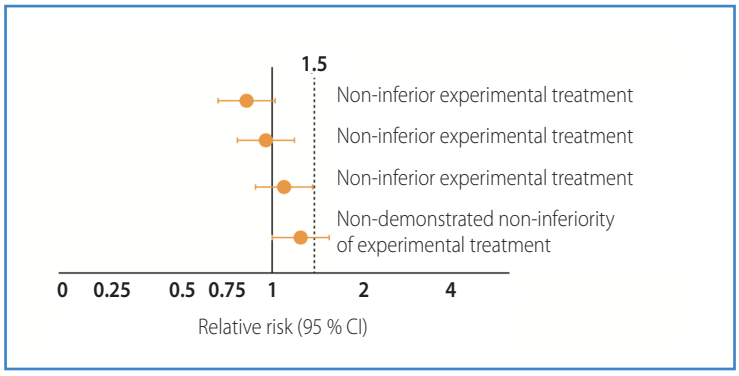

Figure 4. *Example of non-inferiority interpretation.*

- *Delta value:* This is the maximum clinically acceptable difference to define 2 treatments with a tolerable margin for worse outcomes in exchange for other benefits. For example, one chemotherapy may be slightly inferior to a different one, but if the first one has no side effects, we would say that the first drug is non-inferior.
- *Analysis of variables:* The analysis often performed is "per-protocol." This analysis allows for increasing the differences between treatments, making it difficult to conclude that 2 treatments are equivalent, thus maintaining a cautious position when interpreting the results.

Figure 4 illustrates an example of a non-inferiority diagram with various possibilities. The experimental drug is considered better than the control if RR < 1. However, in non-inferiority studies, even if the RR is slightly higher, as long as it does not exceed delta, we would still consider it non-inferior. In other words, in exchange for the experimental drug not being as good as the control, it offers advantages such as fewer side effects, oral administration, or administration every 24 hours instead of every 6 hours, among others.

As we can see, CTs can be as simple or as complex as needed. We should understand what they entail and the design options they offer so that, as researchers, we can choose the one that best suits our study.

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