Acta Medica Colombiana
ISSN: 0120-2448
Asociacion Colombiana de Medicina Interna

VALENCIA-RICO, CLAUDIA LILIANA
Explanatory and pragmatic clinical trials Methodological differences
Acta Medica Colombiana, vol. 48, no. 2, e5, 2023, April-June
Asociacion Colombiana de Medicina Interna

DOI: https://doi.org/10.36104/amc.2023.2614

Available in: https://www.redalyc.org/articulo.oa?id=163177917005

How to cite
Complete issue
More information about this article
Journal's webpage in redalyc.org

Scientific Information System Redalyc
Network of Scientific Journals from Latin America and the Caribbean, Spain and Portugal
Project academic non-profit, developed under the open access initiative

# Explanatory and pragmatic clinical trials
## Methodological differences

CLAUDIA LILIANA VALENCIA-RICO • MANIZALES (COLOMBIA)

DOI: https://doi.org/10.36104/amc.2023.2614


## Abstract

**Introduction:** clinical trials are experimental studies whose results can lead to the best level of evidence expected for healthcare practice; however, their designs have multiple methodological variants needed to ensure their objectives are met. **Objective:** to describe the methodological aspects to be considered in designing explanatory and pragmatic clinical trials.

**Materials and methods:** a review of the literature including articles published from 2016-2020: original or review articles describing the methodological aspects of clinical trials. The search and selection were performed on Google Scholar, Scopus and PubMed, obtaining a total of 47 articles for the analysis.

**Results:** six relevant methodological aspects show differences in clinical trial design with regard to: the purpose and objective; participant recruitment; participant assignment; masking and/or blinding; data analysis; and internal and external validity.

**Conclusion:** both types of clinical trials currently have benefits and barriers to overcome for their performance in the clinical setting; health researchers must have a detailed understanding of their methodological requirements to enable them to carry out these types of studies more accurately.

**(Acta Med Colomb 2022; 48. DOI: https://doi.org/10.36104/amc.2023.2614).**

**Keywords:** *clinical trials, pragmatic clinical trials, statistical models. (Source: DeCS, BIREME).*

Claudia Liliana Valencia-Rico: Programa de Enfermería, Profesora Universidad Católica de Manizales. Estudiante Doctorado en Ciencias de la Salud, Universidad de Caldas. Manizales (Colombia).
Correspondencia: Claudia Liliana Valencia-Rico. Manizales (Colombia).
E-mail: cvalencia@ucm.edu.co
Received: 22/III/2022 Accepted: 7/II/2023

## Introduction

Clinical trials (CTs) are studies with an experimental design which require the voluntary participation of people in whom various health treatments or interventions are evaluated to determine their efficacy, effectiveness and/or safety. Accordingly, they allow one treatment or intervention to be compared with another, or with a control, to observe its effect or result (1). Clinical trials are critical for the health sciences because they allow safe, evidence-based treatments and interventions to be implemented and more sound decisions to be made, aimed at quality care (2).

From the onset of the CT methodology, it was determined that a randomly selected experimental and control group needed to be used. However, this division has historically been arbitrary, and only beginning in 1920 were CTs carried out under these conditions. Likewise, clinical epidemiology and evidence-based medicine (EBM) have proven to be the main areas contributing to the development of this design (3).

Clinical trials have been considered a paradigm of epidemiological and clinical research, because their methods try to control different variables as much as possible to allow a cause-effect relationship to be established with the least bias possible, proving the validity of the experiment and its potential generalization (4). These properties position them as one of the best levels of health evidence, contributing to decision making for the treatment, prevention, etiology and identification of damage from a disease, as well as determining the prognosis and natural history of a disease (5).

Controlled CTs may be said to have essentially been used in pharmacology (6). However, various health areas like pediatrics, midwifery (7), and cardiology (8), among others, have used the experimental design to show effectiveness through a systematic method that contributes greater evidence for their application.

Clinical trials have increased significantly worldwide, in Latin America, and in Colombia. The report of studies in *Clinical Trials* shows that, as of 2020, a total of 344,320 studies had been conducted in 216 countries, 298,287 of which were experimental studies. The North American continent is the main CT producer (133,378), followed by Europe (81,979) and Asia (35,510). In Latin America, Brazil is reported to be the first CT producer (7,286), followed by Mexico (3,631), Argentina (2,762), Chile (1,614) and Colombia (1,338) (9). With regard to the accelerated growth and increasing application of CTs, some authors state that, while the predominance of these studies has prevailed in North America and Europe, Latin American countries are considered attractive for carrying out CTs due to the following factors: a high population and easily accessible racial diversity, the prevalence of chronic diseases and longevity, high medical standards that make it possible to perform

CTs, and a strong doctor-patient relationship that favors participant retention (10,11).

In any case, the performance of CTs in the different health areas requires dedication, effort and a series of obstacles to be overcome, which in many cases become the reason for their failure. In this regard, aspects like lack of investigator training, costly methods, scarcity or lack of funding, complex and time intensive approval requirements, difficulties in clinical practice application, and barriers to participant recruitment, among others, become challenges that investigators have dealt with through collaborative strategies (generally academic) which allow these studies to be performed (12-14).

Furthermore, CTs' level of evidence may be said to be conditioned by a rigorous methodological process which requires demonstrating internal and external validity. Therefore, their planning and implementation must show evidence of a sample recruitment and selection process, transparent assignment of subjects to the different branches or groups, masking and/or blinding, standard operating procedures and a detailed analysis of both the variables of interest as well as the control variables (15).

Today, in the health sciences, explanatory (or classical) CTs and pragmatic CTs can be carried out, which intend to show outcomes under ideal conditions (for the first) or under usual practice conditions (for the second) (5, 12). Both have different scopes, and therefore their objectives, purpose, recruitment methods, assignment, interventions and analysis differ (16). Back in the 60s, Schwartz and Lellouch stated that each method (explanatory and pragmatic) answers one of two problems which arise when comparing two treatments; in this regard, explanatory CTs are aimed at "understanding these treatments," seeking to discover the differences between the two; while pragmatic CTs are aimed more at the need to "*make a decision"* about applying one treatment versus the other, taking into account the contextual conditions of real practice (17). A current example of the use of these two methods was experienced during the COVID-19 pandemic, which required a rapid study of different treatments (including vaccine production), under the explanatory and pragmatic conditions required by the urgency of controlling the pandemic (18, 19).

Historically, explanatory CTs have had a higher priority in clinical practice and are the gold standard for evidence-based practice. However, many of the healthcare guidelines are based on small, non-conclusive CTs, and therefore some authors do not consider it practical to wait for all the everyday clinical questions to be answered through this type of CT (20). On the other hand, pragmatic CTs account for only 2% of all the CTs performed and, despite this, have achieved relevance based on the premise that their results may translate better and be more useful in regular clinical practice and for those responsible for policy making (21). However, progress is slow toward pragmatism in randomized clinical trials because its methodology is still unknown, and there is insufficient conviction and data, record and clinical procedure organization to increase the degree of pragmatism in CTs. Therefore, both types of CTs can be said to still have advantages and disadvantages; meanwhile, it is essential for healthcare researchers to have a detailed knowledge of their methodological requirements, to be able to perform these studies more accurately.

This article, the result of a narrative review, describes the methodological aspects to be kept in mind in the design of explanatory and pragmatic CTs, which are essential for either of these experimental studies.

## Search materials and methods

The scientific literature in Google Scholar, Scopus and PubMed was reviewed. The following stages were followed to determine the methodology: drafting of a guiding question based on the CT methodological process, identification of descriptors, search for papers in the databases mentioned above, application of filters using the inclusion and exclusion criteria, and analysis of the selected papers.

The following guiding question was used for the search:

**What methodological aspects should be taken into account in designing explanatory and pragmatic CTs?**

The search was performed using a combination of the following descriptors: Clinical Trials, Pragmatic Clinical Trials, Methodology, Models Statistical. The inclusion criteria were: articles published in the last five years (2016-2020), written in any language, derived from research or reviews, and describing methodological aspects to be taken into account for CTs. Articles showing specific CT results on any health topic, editorials, duplicate papers and articles describing the ethical component of CTs were excluded.

A total of 77 papers were found which were filtered by title and abstract, obtaining a sample of 47 articles for analysis. Figure 1 shows the number of articles found and the reasons for exclusion.

## Results

Clinical trials make up a single experimental design, but with many variants. In this regard, the analysis of the selected papers revealed six relevant methodological aspects which show differences in the design of explanatory and pragmatic CTs: 1) the purpose and objective, 2) participant recruitment, 3) participant assignment, masking and/or blinding, 4) intervention, 5) analysis of the data obtained, and 6) internal and external validity (Table 1).

### Purpose and objective

In CT design, the term *"purpose"* refers to the study's nature or matter of concern, while the *"objective"* is related to the intended aim or goal of implementing the treatment or intervention. The purpose of an explanatory CT lies in testing a treatment or intervention under ideal conditions with

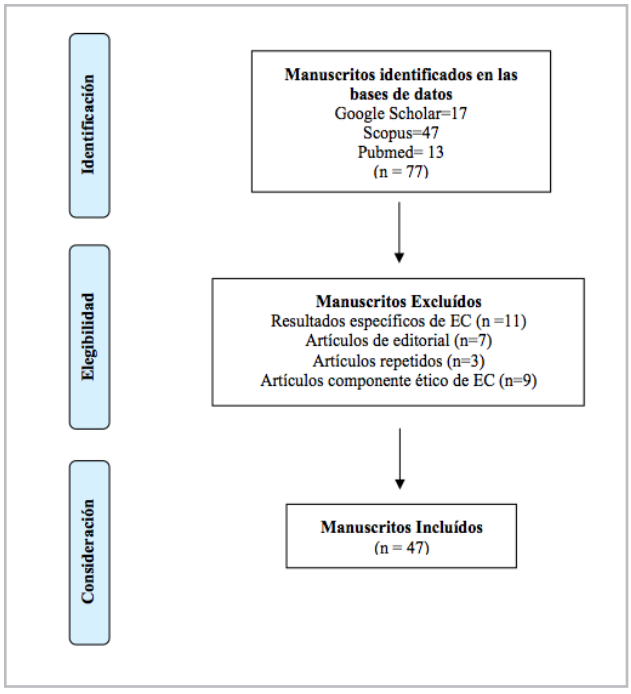


**Figure 1.** *Document search and selection. Source. Own production.*

highly selected participants (19, 20); while its objective is to show the efficacy and/or safety of a controlled treatment in a group of people with similar conditions regarding a health or illness phenomenon (19, 21). In pragmatic CTs, the purpose is similar as far as wanting to test a treatment or intervention, but under usual practice (real) conditions in which a large population of people are cared for (19, 20). The objective of pragmatic CTs is to show not only the effectiveness of the intervention but also its applicability in usual practice settings and in groups of people with diverse conditions (22-24).

## Recruitment

Participant recruitment for CTs is a challenge, as they are often not recruited on time nor with the expected sample size. This may be due to unforeseen problems or an overestimated recruitment rate. There are determinist (conditional and unconditional) and stochastic (Poisson model, Bayesian, simulation model) models for predicting recruitment in the design stage of clinical trials. These models vary considerably in the factors included and their complexity. The determinist models require specification of only a few parameters and, while they are easy to apply, they are likely to be unrealistic. On the other hand, stochastic models allow variation around an average recruitment rate (25).

The most frequently used recruitment methods include social marketing or indirect recruitment (through flyers, pamphlets or web sites) (26) and outreach or direct contact with possible study candidates (27). Along with recruitment, retention strategies are needed to ensure that participants remain in the study. In this regard, successful retention strategies have been used like detailed explanations of the study with its benefits and risks, ongoing contact with the participants through scheduling follow up appointments with reminders, offering flexible appointments, creating a study identity for the patients, assigning recruitment staff with interpersonal skills which show empathy and are culturally competent with the study participants, providing financial incentives and tokens of appreciation for participation (like souvenirs and certificates, in countries where these are legally authorized), involving the community in study design, recruitment and retention (28); and implementing tracking methods for hard-to-reach participants (29). In Colombia, payment for participating in CTs is forbidden by law (10, 30).

Regardless of the type of CT to be implemented, the following three aspects should be kept in mind for strategic recruitment planning: CT design and protocol implementation, the viability and selection of the target institution for the CT, and communication with the people involved (31).

## Participant assignment, masking and/or blinding

The CT sample size allows results to be extrapolated and increases its potential generalization; thus, it is important to determine the representative number of units of analysis to consider in the intervention groups (arms or clusters) (32). The assignment of interventions to the groups of participants may be randomized or nonrandomized. In a randomized CT, the total sample size is a function of both the number of groups and their size. Invariably, one of these is fixed and the others are determined using pre-set formulas. In this case, the intracluster correlation coefficient (ICC) is considered, which measures the degree to which the observations or measurements are correlated within a cluster (33). Random assignment is applied in almost all CTs which compare two or more treatments or interventions with each other. The random element in the assignment process is used to avoid, or at least minimize, the impact of bias on the estimate (or selection) (34).

The statistical factors which predetermine the risk reduction calculation and the number needed to treat are generally related to $\alpha$ (type I) error, $\beta$ (type II) error, the statistical power and the incidence in unexposed groups. These errors may cause false positives or negatives, lead to incorrect rejection of the null hypothesis or to incorrectly estimating the expected frequency of the event in the control group, and to conditioning the expected difference of effect in the outcomes of interest. Therefore, it is important to determine the probability of success based on prior evidence; otherwise, the best option is to establish a 50% probability when prior benchmarks are available (34, 35). To calculate the sample size, the following aspects should be kept in mind: writing a research question, stating the null hypothesis and an alternative hypothesis, selecting the primary outcome measure and the corresponding type of statistical test, considering a range of plausible effects (and variability, if applicable), and

**Table 1.** *Methodological differences between explanatory CTs and pragmatic CTs.*

| Methodological aspect | Explanatory CTs | Pragmatic CTs |
|---|---|---|
| **Recruitment** | Use direct or indirect recruitment methods (27).<br><br>Extensive inclusion and exclusion criteria which may lead to slow recruitment for obtaining participants with the standardized conditions required by the study, with the possibility of becoming clinical and structural barriers to performing the study (56, 57). | Use mostly direct recruitment (27).<br><br>Consider fewer inclusion and exclusion criteria; however, these criteria must be adapted to the CT application setting (22). Recruitment is difficult in critical areas (like the emergency room), especially in obtaining informed consent, as rapid or immediate treatment is needed, with no possibility, in many cases, of postponing treatment (58).<br>Prefer to select a variety of implementation sites in order to ensure that the design includes a range of settings and clinical and demographic characteristics of the patients who are pertinent to the research issue (48, 59). |
| **Participant assignment, masking and/or blinding** | The sample size is extremely important, and the way it was calculated must be shown, taking into account the target population (24). It warrants an intentionally homogenous sample to maximize the treatment effect (60).<br><br>Implies strict random assignment of the participants to the groups or arms, applying informed consent (60).<br><br>Uses masking and/or blinding to show bias control (24, 60, 61). Utiliza enmascaramiento y/o cegamiento para demostrar el control de sesgos (24, 60, 61).<br><br>Use a control group and, at times, a placebo, depending on the objective and purpose of the study (62, 63). Utilizan grupo control y en ocasiones placebo, dependiendo del objetivo y propósito del estudio (62, 63). | The sample size determination may or may not be shown, depending on the objective. Normally, if a sample size is determined, this is done based on the smallest difference considered significant by the investigator who makes the decisions about the objective (24). They seek a diverse and representative sample of the population in the treatment to be evaluated (60).<br><br>May entail individual randomization and the application of informed consent; however, some are based on "group" randomization, in which units (or groups) of participants, like hospitals, clinics and counties, are the randomization unit. In this case, the analysis can be done by "clusters" or participant-level data. On the other hand, the use of group designs may be logistically easier from a participant recruitment perspective, but less statistically efficient due to the correlation between the participants within a group (40,60).<br><br>There is generally no masking or blinding (24,60,61).<br><br>Controls and placebos are not used. They are based on the clinical practice standard (49). |
| **Intervention protocols** | The protocol determines the level and timing of the test and is conducted by investigators trained in the intervention or treatment (60, 61). May be carried out using an adaptive (64, 65) or sequential (66) design, or a master protocol (67).<br><br>Follow up through visits established by the protocol, with strict monitoring (60, 61).<br><br>The intervention lasts for a specific period of time (48).<br><br>Data are gathered exclusively from the evaluations and interventions performed, using validated instruments. Data collection of both the variables of interest as well as confounding variables is required (61). | The protocol is carried out according to the standard of practice and may be conducted by different professionals with limited research experience (40, 60, 61).<br><br>Follow up through visits at the physician's and patient's discretion. Passive or indiret monitoring is allowed (60, 61).<br><br>The intervention may be relatively short, but data collection in all the groups or units may spread out over long periods of time (48).<br><br>Data collection may be scant, and there are few clinical variables through which patient subgroups may be identified. Data may be collected through the intervention performed or the medical chart and from other sources, but this usually means inconsistent data collection and missing data (40, 48, 60). |
| **Data analysis** | Greater control over confounding variables and able to show statistically significant results (24, 43, 44). | Requires a balance between controlling the confounding variables and being realistic about the complex patient populations and clinical conditions in which an intervention must function in the real world (24, 68).<br><br>Less control over confounding variables, but with more clinically significant results (24, 68).<br><br>Must describe where it lies on the continuum between controlled and pragmatic studies and justify each decision in which control is given up to allow for feasibility and general applicability (24). |

selecting the type I or II error based on the objective, clinical considerations and/or phase of the study. This calculation can be done using statistical packages available online which have formulas for each statistical model (36).

Further, the concept of masking or blinding can be mentioned as interchangeable terms to show the concealment of interventions from both the participants as well as the investigators, to reduce measurement bias (37). In this regard, it is important to specify that blinding refers to concealing information (for example, the initial results of an assessment prior to the intervention), while masking refers to concealing the treatments or interventions.

**Intervention**

Treatments or interventions are implemented in each CT, depending on its design. In this regard, various designs have been classically implemented over time to allow the experiment to be applied through different groups: parallel (simultaneous experiments in a series of groups), crossover (with the treatment and control in the same participant), paired (the participants are combined in pairs according to certain characteristics), withdrawal (initial participation in a treatment, followed by random assignment to continue with the treatment or receive a placebo), and factorial (evaluating several interventions in a single trial without increasing the sample size, as long as the treatments function independently) (35, 38). For randomized CTs, the current literature also shows adaptive designs (34, 39) (which allow for evaluation of preliminary results at intermediate points of the intervention or treatment, to modify the study design). For pragmatic CTs, sequential multiple assignment designs are currently cited (mentioned?) (40, 41) (which compare two or more alternative interventions, incorporating a second randomization stage; in this way, the interventions are sequenced based on the person's response).

**Data analysis**

The primary and secondary results analysis plan should be specified before beginning the study. There are two basic types of analysis in CTs, according to the proposed objectives. One is the analysis according to the protocol, in which results are ideally obtained from participants who successfully concluded the treatments or interventions implemented; and the analysis by intention to treat, for those who only completed part of the treatment or intervention. This second type of analysis is important in that it can show the actual effectiveness of the intervention evaluated with just a few sessions (42-44).

The measures of association to be used in CTs are relative risk (RR), as they are prospective studies. In this case, RR is considered as the ratio of absolute risks between the group of individuals exposed to the intervention and those not exposed. When the RR is equal to 1, it is interpreted as there being no association between the intervention and the outcome; therefore, the resulting confidence intervals do not include the unit. When the figure obtained is greater than 1, it means that it is likely that the expected outcome will occur after the intervention is implemented; on the other hand, if it is less than 1, this likelihood decreases. The interpretation of a favorable or unfavorable outcome should be kept in mind in terms of the variable being measured (for example, an RR greater than 1 will be favorable if some risk factor is expected to be reduced, but unfavorable if mortality is what is being measured) (45). Another measure of association is the odds ratio (OR), or risk reduction, which shows the differences between the intervention group and the control group. The CTs which try to measure efficacy clarify the risk reduction using this measure of association.

Relative risk reduction (RRR) corresponds to the difference in risk between the two groups compared with the control group. The problem with using RRR is that it cannot evaluate the real effect if the rate of events in the control group is unknown (45, 46). Finally, the number needed to treat (NNT) is taken as the measure which represents the number of patients who would need to be treated to avoid an adverse event (46, 47).

Finally, in the interpretation of the results, it is essential to distinguish between a statistically significant and clinically significant difference. A difference may be significant from a statistical standpoint but have little clinical value or impact.

**Internal and external validity**

The validity of a CT represents the likelihood of its being bias-free. Internal validity shows the proximity to the truth sought in the results obtained. Thus, to achieve internal validity, the design must show coherence in its question or hypothesis, objectives, uniform characteristics of the participants, correct calculation of the sample size and control of confounding variables (24, 48, 49). High internal validity means that the differences found between the groups are related to the intervention tested in the trial; this means that the study's final outcome is a result of the treatments or interventions implemented and not of other factors. In summary, the internal validity of a CT is directly related to the design, implementation and presentation of appropriate study reports. The two main threats to internal validity are bias and random error. Bias refers to a systematic error which leads to a deviation of the results. The typical sources of bias are data collection, statistical analysis or data interpretation errors; this leads to the actual difference between the study groups possibly being under or overestimated. The four main sources of bias in clinical trials are selection bias (controlled with randomization), performance bias (controlled through adequate adherence to the treatment or intervention and controlling for confounding variables), detection bias (controlled by blinding) and burnout or attrition bias (controlled through the intention to treat analysis) (35).

On the other hand, external validity helps show to what extent the results obtained are generalizable and can be applied to populations similar to those of the study (24, 48, 49).

It should be noted that internal validity is a prerequisite for a study to have external validity. If the inclusion and exclusion criteria are carefully established, specific study samples can be selected, but there is also a risk of jeopardizing the generalization (35).

To improve the transparency of clinical trials, databases like *ClinicalTrials.gov* (9) have been created to follow the changes between the planned and published studies, and to keep investigators up to date on the ongoing clinical trials. The studies must be registered in these databases before enrolling the first participant. Most medical journals request registry in a study database as a prerequisite for publication.

Furthermore, as a quality measure, standards have been consolidated for presenting trial reports. For instance, there is the CONSORT declaration, which is a tool that standardizes all the aspects to consider for publishing a CT. CONSORT consists of five domains made up of 22 items which help generate a structured report of the following aspects: title/abstract, introduction, methods, results and discussion. It also has a flow chart to describe the CT stages (50). The objective of the CONSORT declaration is to prevent incomplete CT information and show validity and reliability, which challenges the authors to fully comply with this standard (51). Some specific areas of knowledge have their own extensions in this declaration, which are constantly updated and complemented, with the aim of achieving greater accuracy in study reporting (52, 53).

Pragmatic CTs also have the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) as a tool to quantify the degree to which a CT incorporates pragmatic principles. It is advisable for investigators to self-assess the degree of pragmatism of their proposed trial using this tool.

The PRECIS-2 consists of nine criteria (eligibility, recruitment, adjustment, organization, delivery, adherence, follow up, primary outcome and primary analysis). Each criterion has a Likert scale score of 1 to 5, with 1 being a very explanatory trait and 5 being the highest pragmatic trait (54, 55).

## Discussion

As has been indicated, CTs are experimental studies whose characteristics vary according to their design. Explanatory CTs have an important role, but interventions in clinical practice rarely fit the strictly controlled environment of this type of study, while pragmatic CTs create the possibility of applying treatments and interventions in routine practice (21).

Recruitment clearly does not only depend on the strategies implemented by the research team, but also on the clinical and structural barriers which increase or decrease the possibility of participant enrollment and retention. In this regard, a meta-analysis of cancer CTs showed that more than half (55.6%) of cancer patients do not participate in CTs because there are none available for their type of cancer or the stage which is being treated, and when a trial is available, an additional 21.5% is not eligible. Taken together, these structural and clinical factors are the reason why more than three out of four patients (77.1%) do not participate (57). All the same, the participation of patients and the public in CT enrollment and retention has been shown to lead to a modest improvement in enrollment when organized recruitment strategies are implemented, especially when people with prior experience with the study's health condition are included (28).

On the other hand, the methodological rigor of CTs may also lead to participant dropout, given the many improvisations which may occur in the implementation of these studies. In this regard, it has also been proven that the dropout rate in some CTs is greater when they have low methodological quality or when there are technical errors, more than due to the effects of the treatments themselves (69).

Regarding sample size and cluster assignments, the investigators have several options when faced with a limited number of groups and a predetermined intracluster correlation coefficient (ICC) indicating that very large cluster sizes may be required to reach the desired power. In this case, the recommended option would be to increase the number of groups, if possible. Otherwise, a decision must be made between having a smaller group size without achieving the ideal (33). These situations may lead to errors in participant randomization; one of the most common errors is involuntary randomization of ineligible participants, especially in Phase III CTs. Less often, people who are suitable for the CT and willing to participate are not randomized. Both errors are serious, both for the person to whom the treatment is administered without meeting the eligibility criteria as well as for the loss of participants who, while suitable for the study, are not chosen. The biggest aggravating factor is the fact that there is very little reporting of these errors in the publications and the CTs do not clearly described the methods used for the randomization sequence, which makes it even more difficult to perceive these errors (70)

There are significant differences in the application of the intervention protocols in explanatory and pragmatic CTs. Therefore, it is important to clarify that neither design is better than the other; each simply specifies a desirable intervention or treatment under different conditions, with different objectives, which allows different results in each case, but both contributing to the clinical setting. Thus, each CT will need to clearly specify the explanatory or pragmatic characteristics and their respective analysis, to show how well the therapies work in a routine care setting versus the ideal (60). The objective of each CT can be said to lead to a different primary outcome; one example would be spine surgery, with noticeable differences in that an explanatory CT can show the primary outcome of physical function through the walking ability gained and the performance of physical tasks, while the primary outcome of the pragmatic CT evaluates the degree of disability, including assessment of pain intensity and the impact of symptoms on the patients'

social life, sex life, and ability to travel, in addition to the ability to perform physical tasks (21). Consequently, pragmatic CTs not only determine the efficacy of the treatment, but also its effectiveness, evaluated from different individual, family and social aspects which impact people's lives and are improved through the intervention performed.

Today, an increased use of pragmatic clinical trials is advocated in nursing and the various healthcare areas, in general. A sequential multiple assignation randomized trial (SMART) is a valuable design which is currently receiving more attention in nursing because it provides pertinent clinical trials using the comparison of two or more alternative interventions, incorporating a second stage of randomization based on the person's response (40). In this regard, the sequential design becomes essential evidence for the nursing process because it identifies which of the interventions work better, the ideal sequence of interventions for the general population, and in which type of population they function most effectively.

On the other hand, it should be noted that there is a subclass of pragmatic CTs whose results are derived from registries and clinical charts which describe the interventions carried out in actual practice. Essentially, this type of study is attractive because it is inexpensive, since it saves on costly interventions, time investment and qualified staff. However, there is often minimal control over which data to collect and how to do so, and therefore investigators face challenges in methodologically specifying how to handle incomplete, missing or inconsistent data (40, 60).

Even if pragmatic CTs are presented as a savior to bridge the existing gap between the controlled requirements of explanatory studies and the scant possibility of their application in the real world, it must be recognized that a current disadvantage of pragmatic CTs is their scarce publication, in which specific guidelines must be met to prove the level of pragmatism. Thus, it is a challenge to write and publish a pragmatic CT, as it must prove to what degree the variables were controlled and the level to which the intervention was allowed to advance to show its effectiveness, regardless of the diversity of the participants. The major challenge for investigators is to specify the method used, since there is no standardized methodological rubric to guide pragmatic CTs, as there is for explanatory CTs.

Some specific health specialties have evolved from the explanatory level to pragmatism over time. One specific case can be seen in cardiology, where the level of pragmatism has increased moderately, showing more flexibility in aspects like participant eligibility, target institutions, the interventions and the primary outcome. Thus, over a five-year period, pragmatic cardiology CTs had more intervention implementation sites, larger sample sizes, longer follow-up, and mortality as the primary final outcome (71).

## Conclusion

Both types of CTs can be said to be beneficial today, and both must overcome barriers to their implementation in the clinical setting. Internal and then external validity are directly related to the design, implementation and presentation of adequate study reports. The methodological evolution of CTs calls for small efficacy studies to be increasingly applied in larger settings to achieve the potential for generalization which will help improve decision making in health care and, thus, healthcare quality.

## References


1. **Cuevas Pérez O, Molina Gómez A, DR FR.** Los ensayos clínicos y su impacto en la sociedad. *Medisur.* 2016;14(1):13-21.
2. **Brito-Pérez K, Cañete-Villafranca C, del Puerto-Horta MG-LM.** Algunas consideraciones relacionadas con los ensayos clínicos. *Rev Med Electrón*. 2016;**38(5):**719–24.
3. **Котеров А, Тихонова О, Ушенкова Ј, Бирюков А.** History of controlled trials in medicine: Real priorities are little-known. Report 1. Basic concepts, terms, and disciplines that use medical experiment: Historical and philosophical sources. 2021;**14(1):**72-98. doi: 10.17749/2070-4909/FARMAKOEKONOMIKA.20.
4. **Ahumada V, Torrez D.** El ensayo clínico como método de investigación. *Rev Chil Anest*. 2014;43:327–31.
5. **Manterola C, Quiroz G, Salazar P, García N.** Metodología de los tipos y diseños de estudio más frecuentemente utilizados en investigación clínica. *Rev Med Clin Condes*. 2019;**30(1):**36-49. doi: 10.1016/j.rmclc.2018.11.005.
6. **Cartes-Parra J.** Breve historia de la tuberculosis. *Rev Médica Costa Rica y Centroam*. 2013;LXX(605):145–50.
7. **Demirdjian G.** Historia de los ensayos clínicos aleatorizados. *Arch.Argent.Pediatr.* 2006;**104(1):**58-67.
8. **Tomberli B, Mattesini A, Baldereschi G, Di Mario C.** Breve historia de los stents coronarios. *Rev Española Cardiol*. 2018;**71(5):**312-319. doi: 10.1016/j.recesp.2017.11.016.
9. **U.S National Library of M.** Clínical Trials.gov. 2020 [Internet]. Disponible en: https://clinicaltrials.gov/ct2/search/map
10. **Molina de Salazar, DI Botero S, Giraldo G.** Investigación clínica y ensayos clínicos ¿En qué vamos? *Acta Médica Colomb*. 2016;**41(3):**43–50.
11. **Rocha de Oliveira, R d'Ávila Viana A.** Expansão global dos ensaios clínicos: inovação e interação. *Cad. Saúde Pública*. 2019;**35(11):e**00063518. doi: 10.1590/0102-311X00063518.
12. **De la Torre Hernández J, Edelman E.** De la investigación no clínica a los ensayos y registros clínicos: retos y oportunidades en la investigación biomédica. *Rev Esp Cardiol*. 2017;**70(12):**1121-33. doi: 10.1016/j.recesp.2017.07.017.
13. **Gil-Extremera B, Jiménez-López, P Mediavilla-García J.** Ensayos clínicos. Una asignatura pendiente. Rev Clin Esp. 2017;**2018(3):**137-141. doi: 10.1016/j.rce.2017.06.006.
14. **Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt S, et al.** Barriers to the conduct of randomized clinical trials within all disease areas. Djurisic et al. *Trials*. 2017;**18(1):**360. doi: 10.1186/s13063-017-2099–9.
15. **Amar B, Prakesh S, Shah GA.** A simplified guide to randomized controlled trials. *Acta Obstet Gynecol Scand*. 2018;**97:**380-87. doi: 10.1111/aogs.13309.
16. **Cartabellotta A.** Trial controllato randomizzato: un disegno, numerose varianti. Guida all'articolato linguaggio dei trial (II). *AMD*. 2011;**14:**211–4.
17. **Schwartz D, Lellouch J.** Explanatory and pragmatic attitudes in therapeutical trials. J *Chronic Dis*. 1967;**20(8):**637–48.
18. **Carracedo S, Palmero A, Neil M, Hasan-Granier A, Saenz C, Reveiz L.** El panorama de los ensayos clínicos sobre COVID-19 en América Latina y el Caribe: evaluación y desafíos. *Rev Panam Salud Publica*. 2021;**45**:e33. DOI: 10.26633/RPSP.2021.33.
19. **Alqahtani M, Mallah SI, Stevenson N, Doherty S.** Vaccine trials during a pandemic: potential approaches to ethical dilemmas. *Trials*. 2021;**22(1):**628. DOI: /10.1186/s13063-021-05597–8.
20. **Rodriguez F, Califf R, Harrington R.** Consequences of SlowProgress Toward Pragmatism in Randomized Clinical Trials It Is Time to Get Practical. *JAMA Cardiol*. 2019;**4(11):**1129-30. doi: 10.1001 / jamacardio.2019.3922.
21. **Delitto A.** Pragmatic Clinical Trials: Implementation Opportunity, or Just Another Fad? *Phys Ther.* 2016;96(2):137-38. doi: 10.2522/ptj.2016.96.2.137.
22. **Merali Z, Wilson J.** Explanatory Versus Pragmatic Trials: An Essential Concept in Study Design and Interpretation. *Clin Spine Surgx*. 2017;**30(9):**404-06. doi: 10.1097 / BSD.0000000000000588.
23. **Veit K, Vassar M, Homas J.** A Descriptive Analysis of Registered Pragmatic Clinical Trials. Oklahoma State Univ. 2018;**1(3)**:p4.
24. **Pickler R, Kearney M.** Publishing pragmatic trials. Nursing Outlook. 2018; *Nurs Outlook*. 2018;**66(5**):464-69. doi: 10.1016/j.outlook.2018.04.002.

25. **Gkioni E, Rius R, Dodd S, Gamble C.** A systematic review describes models for recruitment prediction at the design stage of a clinical trial. *J Clin Epidemiol*. 2019;**115:**141-49. doi: 10.1016/j.jclinepi.2019.07.002.
26. **Brogger-Mikkelsen B, Ali Z, Zibert J, Andersen A, Thomsen S.** Online Patient Recruitment in Clinical Trials: Systematic Review and Meta-Analysis. *J Med Internet Res*. 2020;**22(11):**e22179. doi: 10.2196/22179.
27. **Caldieraro-Bentley, AJ Kelechi T, Treat-Jacobson D, Mueller M**. Challenges in recruitment of persons with peripheral artery disease for exercise studies. *J Vasc Nurs*. 2018;**36(3):**111-20.doi: 10.1016 / j.jvn.2018.03.003.
28. **Crocker J, Ricci-Cabello I, Parker A, JA H, Chant A, Petit-Zeman S, et al.** Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. *BMJ* 2018. 2018**;363**:k4738. doi: 10.1136/bmj.k4738.
29. **Kaiser B, Thomas G, Bowers B.** A Case Study of Engaging Hard-to-Reach Participants in the Research Process: Community Advisors on Research Design and Strategies (CARDS). *Res Nurs Health*. 2017;**40:**70-9. doi: 10.1002/nur.21753.
30. **Parkinson B, Meacock R, Sutton M, Fichera E, Mills N, Shorter G, et al.** Designing and using incentives to support recruitment and retention in clinical trials: a scoping review and a checklist for design. *Trials*. 2019;**20**:624. doi: 10.1186/s13063-019-3710-z.
31. **Huang G, Bull J, Johnston K, Mahon E, Harper B, Roberts J, et al.** Clinical trials recruitment planning : A proposed framework from the Clinical Trials Transformation Initiative. *Contemp Clin Trials* [Internet]. 2018;66:74-79. doi: https://doi.org/10.1016/j.cct.2018.01. Disponible en: https://doi.org/10.1016/j.cct.2018.01.003
32. **Otzen T, Manterola C.** Técnicas de Muestreo sobre una población a estudio. Int J Morphol. 2017;**35(1)**:227-32. doi: 10.4067/S0717-95022017000100037.
33. **Hemming K, Eldridge S, Forbes G, Weijer C, M T.** How to design efficient cluster randomised trials. *BMJ*. 2017;**358:**j3064. doi: 10.1136/bmj.j3064.
34. **Ralf-Dieter, Hilgers Malgorzata B, Carl-Fredrik, Burman Holger D, Mats K, Franz K.** Lessons learned from IDeAl-33 recommendations from the IDeAl-net about design and analysis of small population clinical trials. *Orphanet J Rare Dis*. 2018;**13:**77. doi: 10.1186/s13023-018-0820–8.
35. **Spieth P, Kubasch A, Penzlin A, Min-Woo I, Barlinn K, Siepmann T.** Randomized controlled trials – a matter of design. *Neuropsychiatr Dis Treat*. 2016;**12:**1341-49. doi: 10.2147/NDT.S101938.
36. **Sigrun A J S, Serigne L, Loes M H.** Research Techniques Made Simple: Sample Size Estimation and Power Calculation. *J Invest Dermatol*. 2018;**138:**1678-82. do: 10.1016/j.jid.2018.06.165.
37. **Grayling M, Mander A, Wason J.** Blinded and unblinded sample size reestimation in crossover trials balanced for period. *Biometrical J*. 2018;**60(5):**917-33. doi: 10.1002/bimj.201700092.
38. **Kahana B, Tsuib M, Jairathc V, Mae-Scotte A, Altmanf D, Beller E, et al.** Reporting of randomized factorial trials was frequently inadequate. *J Clin Epidemiol*. 2020;**117:**52-9. doi: 10.1016/j.jclinepi.2019.09.018.
39. **Bothwell L, Kesselheim A.** The Real-World Ethics of Adaptive-Design Clinical. *Hast Cent Rep*. 2017;**47(6):**27-37. doi: 10.1002 / hast.783.
40. **Doorenbos A, Kato Y.** Pragmatic clinical trials: Increasing the rate of translating nursing research into practice. *Jpn J Nurs Sci*. 2020;e12350. doi: 10.1111/jjns.12350.
41. **Molina-Arias M.** Diseños secuenciales: interrupción precoz del ensayo clínico. *Rev Pediatr Aten Promaria*. 2017;**19:**87–90.
42. **Pocock S, McMurray J, TJ. C.** Statistical Controversies in Reporting of Clinical Trials. *JACC*. 2015;**66:**2648-62. doi: 10.1016/j.jacc.2015.10.023.
43. **Johnston B, Guyatt G.** Best (but oft-forgotten) practices: intention-to-treat, treatment adherence, and missing participant outcome data in the nutritional literature. *Am J Clin Nutr*. 2016;104(5):1197-1201. doi: 10.3945 / ajcn.115.123315.
44. **Zixiao L, Xianwei W, Huiman Xie, Barnhart Yongjun W.** Working With Statisticians in Clinical Research. *Stroke*. 2018;*49*:e311-e313. doi: 10.1161/STROKEAHA.118.022266.
45. **Estrada S, Arancibia M, Stojanova J, Papuzinski C.** Conceptos generales en bioestadística y epidemiología clínica: estudios experimentales con diseño de ensayo clínico aleatorizado. *Medwave* 2020. 2020;**20(2)**:e7869. doi: 10.5867/medwave.2020.02.7869.
46. **Ranganathan P, Pramesh C, Aggarwal R.** Common pitfalls in statistical analysis: Absolute risk reduction, relative risk reduction, and number needed to treat. *Perspect Clin Res*. 2016;**7(1):**51-3. doi: 10.4103/2229-3485.173773.
47. **Lajoie A, Bonnet S, Lacasse Y, Lega J.** Provencher S. Interpreting risk reduction in clinical trials for pulmonary arterial hypertension. *Eur Respir Rev*. 2018;**27:**180020. doi: 10.1183/16000617.0020-2018.
48. **Sox H, Lewis R.** Pragmatic Trials Practical Answers to "RealWorld" Questions. *JAMA*. 2016;316(11):doi: 10.1001 / jama.2016.11409.
49. **Neta G, Johnson K.** Informing real-world practice with real-world evidence: the value of PRECIS-2. *BMC Med*. 2018;**16:**76. doi: 10.1186/s12916-018-1071–1.
50. **Castaño-García A, Guillén-Grima F, León-Sanz P.** Valoración de la calidad metodológica y ética de los ensayos clínicos publicados en revistas de medicina de familia (2010-2013). *Gac Med Mex*. 2018;**154:**92-104. doi: 10.24875/GMM.17002699.
51. **Ghosn L, Boutron I, Ravau P.** Consolidated Standards of Reporting Trials (CONSORT) extensions covered most types of randomized controlled trials, but the potential workload for authors was high. *JCE*. 2019;**113:1**68-75. doi: 10.1016/j.jclinepi.2019.05.030.
52. **Grant S, Mayo-Wilson, E Montgomery P, Macdonald G, Michie S, Hopewell S, Al. E.** CONSORT-SPI 2018 Explanation and Elaboration: guidance for reporting social and psychological intervention trials. *Trials*. 2018;**19:**406. doi: 10.1186/s13063-018-2735-z.
53. **Jiang L, Jia-yuan H, Jing-bo Z, Jun-qiang N, Joey S.W K, Long G, et al.** CONSORT extension for reporting N-of-1 trials for traditional Chinese medicine (CENT for TCM): Recommendations, explanation and elaboration. *Complement Ther Med*. 2019;**46:**180-88. doi: 10.1016/j.ctim.2019.08.014.
54. **Groenwold R, Dekkers O.** Designing pragmatic trials – what can we learn from lessons learnt? *J Clin Epidemiol*. 2017;doi: 10.1016/j.jclinepi.2017.06.006.
55. **Loudon K, Zwarenstein M, Sullivan F, Donnan P, Gágyor I, Hobbelen H, et al.** The PRECIS - 2 tool has good inter - rater reliability and reasonable discriminant validity. *J Clin Epidemiol*. 2017;doi: 10.1016/j.jclinepi.2017.06.001.
56. **Feldman W, Kim A, Chiong W.** Trends in Recruitment Rates for Acute Stroke Trials, 1990–2014. *Stroke*. 2017;**48(3):**799-801. doi: 10.1161/STROKEAHA.116.014458.
57. **Unger J, Vaidya R, Hershman D, Minasian L, Fleury M.** Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. *JNCI J Natl Cancer Inst*. 2019;**111(3)**:djy221. do: 10.1093/jnci/djy221.
58. **García Arenillas M, Haj-Ali Saflo O, Sáenz de Tejada M.** Principales implicaciones del nuevo Real Decreto de ensayos clínicos para los urgenciólogos investigadores. *Emergencias*. 2017;**29:**194–201.
59. **Worsley S, Oude Rengerink K, Irving E, Lejeune S, Mol K, S C.** Challenges in Pragmatic Trials: Selection and Inclusion of Usual Care Sites. *Journal of Clinical. Epidemiology*. 2017;**88:**14-20. doi: 10.1016/j.jclinepi.2017.05.003.
60. **Rockhold F, Goldstein B.** Pragmatic Randomized Trials Using Claims or Electronic Health Record Data. *Trials*. 2018;**278:**19. doi: 10.1007/978-3-319-52677-5_270-1.
61. **Mentz R, Hernandez A, Berdan L, Rorick T, O'Brien E, Ibarra J, et al.** Good Clinical Practice Guidance and Pragmatic Clinical Trials: Balancing the Best of Both Worlds. *Circulation*. 2016;**133(9):**872–80. doi: 10.1161/CIRCULATIONAHA.115.019902.
62. **Colloca L.** The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol*. 2019;59:191–211. doi: 10.1146/annurevpharmtox-010818–02154.
63. **Phaik Yeong, Cheah Norbert S, Lorenz von S, Ric N P.** The ethics of using placebo in randomized controlled trials: a case study of a Plasmodium vivax antirelapse trial. *BMC Med Ethics*. 2018;19:19. doi: 10.1186/s12910-018-0259–4.
64. **Burnett T, Mozgunov P, Pallmann P, Villar S, Wheeler G, Jaki T.** Adding flexibility to clinical trial designs : an example-based guide to the practical use of adaptive designs. *BMC Med*. 2020;18:352. doi: 10.1186/s12916-020-01808–2.
65. **Sarkar S, Srivastava V, Patanayak C.** Adaptive designs in clinical trials. *Pharmacol Pharmacother*. 2020;**11(4):**129-133. doi: 10.4103/jpp.JPP_79_20.
66. **Gao L, Zhu H, Zhang L.** Journal of Statistical Planning and Inference Sequential monitoring of response-adaptive randomized clinical trials with sample size re-estimation. *J Stat Plan Inference* [Internet]. 2020;**205:**129-137. doi: 10.1016/j.jspi.2019.06.007. Disponible en: https://doi.org/10.1016/j.jspi.2019.06.007
67. **Meyer E, Mesenbrink P, Dunger-Baldauf C, Fülle H, Ekkehard G, Li Y, et al.** The Evolution of Master Protocol Clinical Trial Designs : A Systematic Literature Review. *Clin Ther*. 2020;**42(7):**1-31. 1330-60. doi: 10.1016 / j.clinthera.2020.05.
68. **Rockhold F, Tenenbaum J, Richesson R, Marsolo K, O'Brien E.** Design and analytic considerations for using patient-reported health data in pragmatic clinical trials: report from an NIH Collaboratory roundtable. *J Am Med Inf Assoc*. 2020;**27(4):**634-38. doi: 10.1093/jamia/ocz226.
69. **de Campos Moreira, T Dalbosco-Gadenz, C Capobianco D, Rizzieri-Figueiró, L Ferigolo M, Vissoci J, Al. E.** Factors Associated With Attrition in Randomized Controlled Trials of Vocal Rehabilitation: Systematic Review and Meta-Analysis. *J Voice*. 2017;**31(2):**259.e29-259e40. doi: 10.1016/j.jvoice.2016.05.014.
70. **Yelland L, Kahan B, Dent E, Lee K, Voysey M, Forbes A, et al.** Prevalence and reporting of recruitment , randomisation and treatment errors in clinical trials : A systematic review. *Clin Trial*. 2018;**15(3)**:278-85. doi: 10.1177/1740774518761627.
71. **Nariman, Sepehrvand Wendimagegn A, Debraj D, Arjun K G, Pishoy G, Anukul G, Al E.** Trends in the Explanatory or Pragmatic Nature of Cardiovascular Clinical Trials Over 2 Decades. *JAMA Cardiol* 2019. 2019**;4(11):**1122-28. doi:10.1001 / jamacardio.2019.3604.