



# On the Methodological Aspects of the Clinical Trials for COVID-19 Conducted in the First Year of the Pandemic: A Descriptive Analysis

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## Abstract

In 2020, the whole planet was plagued by the extremely deadly COVID-19 pandemic. More than 83 million people had been infected with COVID-19 while more than 1.9 million people around the planet had died from this virus in the first year of the pandemic. From the first moment, the medical community started working to deal with this pandemic. For this reason, many clinical trials have been and continue to be conducted to find a safe and efficient cure for the virus. In this paper, we review the 96 clinical trials, registered in the ClinicalTrials.gov database, that had been completed by the end of the first year of the pandemic. Although the clinical trials contained significant heterogeneity in the main methodological features (enrollment, duration, allocation, intervention model, and masking) they seemed to be conducted based on an appropriate methodological basis.

**Keywords** COVID-19 · Clinical trials · Descriptive analysis · Pandemic · Risk of bias · SARS-CoV-2 · Statistical design

## 1 Introduction

The COVID pandemic, or COVID-19 virus, is due to a virus belonging to the family of coronaviruses which was first discovered in 1964 in London by June Almeida [1]. What most viruses in this category can cause is a respiratory infection and in some

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cases even pneumonia. It was 2002 in China when coronavirus caused severe acute respiratory syndrome (known as SARS) until in December 2019 a new type of coronavirus appeared, the one of Wuhan, known as SARS-CoV-2, which is responsible for the pandemic [2, 3].

According to the World Health Organization (WHO), a significantly large number of people were infected (about 83 million) and died from the virus (about 1.9 million) in 2020. For the above reasons, scientists studied how the virus attacks human cells and came to the conclusion that the interaction of glycoprotein ACE2 of the virus in combination with heparin sulfate located in the cell membrane, allows the virus to enter the cell and then begins to multiply [3, 4].

COVID-19 may attack all groups of people in different ways. Most infected people experience mild to moderate symptoms and recover without having to be hospitalized. The most common symptoms include fever, dry cough, and tiredness while more rare symptoms such as pain, diarrhea, conjunctivitis, headache, sore throat, loss of taste or smell, a skin rash, or discoloration on the fingers or toes will occur [5–8]. Based on retrospective studies, which evaluated how various characteristics such as age, gender of men, increased body mass index (BMI), comorbidities including diabetes, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, and hypertension may play a role in virus infection, it was found that there is some positive association with an increased risk of coronavirus infection for people who carry the above characteristics [9]. In addition to these characteristics, environmental as well as genetic factors may also increase sensitivity to COVID-19 [10].

In recent years, it has been widely recognized that properly designed and carefully implemented clinical trials, which follow the principles of scientific experimentation, provide the only reliable basis for evaluating the efficiency and safety of new treatments. Clinical trials are essentially clinical trials involving mostly humans. Conducting an effective and useful clinical study is mainly related to its proper design since in clinical trials there are many aspects that must be taken into account both organizational and ethical.

Several authors have dealt with the methodological or non-methodological characteristics of clinical trials by retrieving data from the ClinicalTrials.gov database. Hirsch et al. [11] studied the characteristics of oncology clinical trials while Chen et al. [12] reviewed the characteristics of traditional Chinese medicine clinical trials. Hill et al. [13] reviewed the characteristics of 284 pediatric cardiovascular clinical trials. Dechartres et al. [14] described the characteristics of completed phase III or IV clinical trials of rare diseases and assessed whether their results were publicly available. Cheng et al. [15] studied the key design characteristics of 53 geographic atrophy clinical trials while Dammo et al. [16] conducted a cross-sectional study to examine the characteristics of 151 studies of pharmacist services. Califf et al. [17] reviewed the fundamental characteristics of 96,346 clinical trials registered in ClinicalTrials.gov in the period 2007–2010. Recently, Pundi et al. [18] evaluated the characteristics and expected strength of evidence of COVID-19 studies.

The aim of this paper is to assess whether the clinical trials for COVID-19 conducted in the first year of the pandemic followed the basic methodological requirements, i.e., enrollment, duration, allocation, intervention model, and masking. The paper is organized as follows. In the second section, we briefly discuss the basic

statistical methodological characteristics of clinical trials. In the third section, we briefly describe the way we retrieved the reviewed clinical trials. In Section 4, we present the basic methodological aspects of these clinical trials, while in Section 5 we critically discuss the results of the study. Concluding remarks are presented in the last section.

## 2 Statistical Characteristics of Clinical Trials

According to Pocock [19], a clinical trial is a randomized trial that aims to evaluate the effectiveness and safety of a treatment. In the case of two or more treatments, the purpose of the clinical trial is to compare the treatments for efficacy and safety.

Clinical trials are classified into four phases [19]. Phase I clinical trials aim mainly at the safety and not the effectiveness of the drug under study. Phase II clinical trials are small-scale (100–200 people) studies on the efficacy and safety of the treatment under test. Once a Phase II clinical trial has shown that a treatment is effective, it should be compared to standard treatment (or treatments) for the same disease or condition. This comparison is made through a large-scale Phase III clinical trial, in which a large number of patients (1000–3000 patients) participate. Finally, once the treatments have been approved and released, there are issues that need to be monitored, mainly in terms of side effects, or additional long-term morbidity or mortality studies. This is the purpose of Phase IV clinical trials.

To achieve an unbiased assessment of the new treatment, it is necessary to adhere to the fundamental statistical principle of *randomization*. According to this, the administration of both the new and the standard treatment to the patients should be done in a random way. Nowadays it is generally accepted that randomized controlled clinical trial is the most reliable way of conducting clinical medical research.

The use of a placebo (i.e., an inert treatment), as well as the comparison of two treatments, allows the *masking* or *blinding* of a medical study. This term refers to which of the parties involved in a clinical trial (participants, care providers, investigators, and outcomes assessors) are unaware of the treatment assigned to participants. The main types of masking are open-label, single-blind masking, and double-blind masking.

Another crucial feature of clinical trials is the calculation of the *sample size*, i.e., the calculation of the number of people who will take part in the trial [20]. In order for the sample size to be valid, it should be calculated on the basis of appropriate statistical tests. There are two ways to calculate the sample size: precision analysis or power analysis. The first is performed by controlling the type I error (or the confidence level) while the latter by controlling the type II error (or the power of the test).

The simplest design for a clinical trial is the *single group assignment*, in which all participants receive the same intervention or treatment. However, in most of the cases, there are two or more groups of participants receiving different interventions [19]. The simplest form of this design is the *parallel assignment*, in which two or more groups of participants receive a different treatment [19]. The *sequential assignment* requires interim analyses, the outcome of which determines whether

additional patients will enter the study or the study will be terminated [19]. In the *factorial assignment* groups of participants receive one of several combinations of treatments [19]. For example, a two-by-two factorial assignment involves four groups of participants, where each group receives one of the four possible pairs of treatments. The most complex study intervention model is *cross-over assignment*, in which groups of participants receive two or more interventions in a specific order [19]. For example, a two-by-two cross-over assignment involves two groups of participants of which one group initially receives treatment A and then treatment B. The second group receives treatment B during the initial phase and then treatment A. All participants receive treatment A and treatment B at some time during the clinical trial, but in a different order, based on the group to which they have been assigned.

### 3 Method

To retrieve the relevant completed clinical trials conducted during 2020 (i.e., the first year of the pandemic), we searched the ClinicalTrials.gov database on March 21, 2022, using the following keywords: COVID-19, Coronavirus, and Coronavirus Infection. Here we should note that ClinicalTrials.gov automatically searched for COVID and SARS-CoV-2 when we used the COVID-19 keyword. ClinicalTrials.gov is a database, provided by the U.S. National Library of Medicine, of both privately and publicly funded clinical studies conducted around the world.

Our search was restricted to the Phase II and III clinical trials because only in these two phases formal statistical designs are applied. After removing duplicates, a total of 96 clinical trials were retrieved and analyzed.

Continuous variables were presented as mean (standard deviation) while categorical variables were presented as absolute (relative) frequencies. The non-parametric Kruskal–Wallis test was used to compare the quantitative characteristics of the clinical trials among their phases and intervention model. The Pearson's chi-square test was performed to assess the association between qualitative variables. The IBM SPSS Statistics 28 and the R language were used for the statistical analysis.

The quality of the clinical trials methodology was assessed through the Cochrane bias risk assessment tool. A total of 6 items were included (i.e., selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias) and each item was identified as either high risk, low risk, or unclear. The assessment was done, by both authors, according to whether the clinical trials provided information about these types of bias.

## 4 Results

### 4.1 Unstratified Analysis

Ninety-six clinical trials for COVID-19 had been completed by the time this survey was conducted. 40 out of 96 clinical trials (41.7%) were large-scale Phase

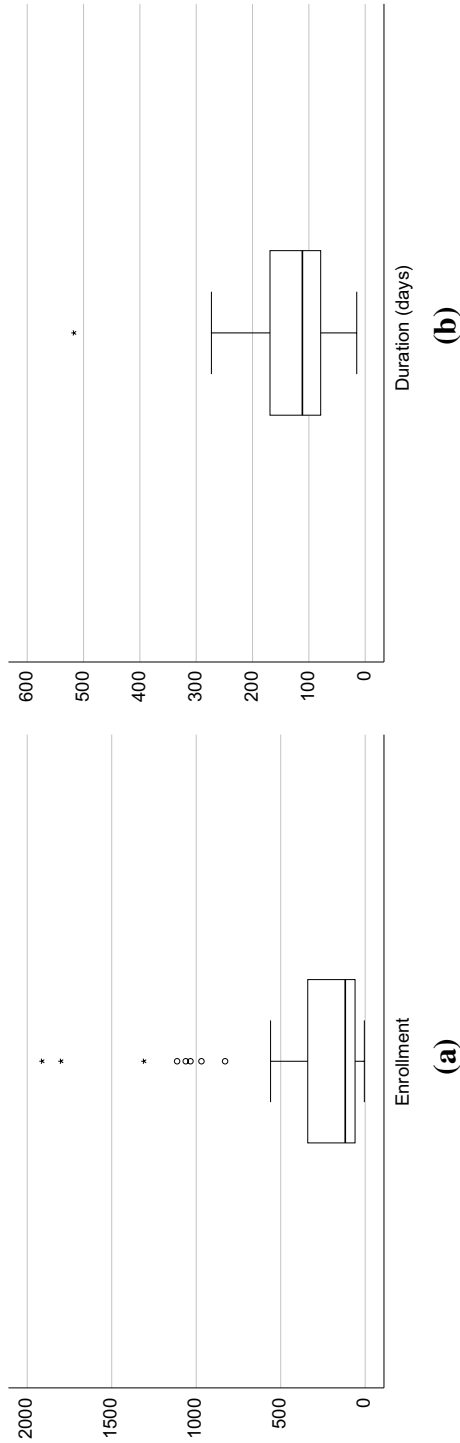
III clinical trials, 40 were small-scale Phase II clinical trials, while 16 (16.7%) were a combination of Phase II/Phase III clinical trials. 84 of the clinical trials were randomized, 6 were non-randomized, and for 6 of them, the allocation was not recorded. 34 out of the 40 Phase II clinical trials, 15 out of the 16 Phase II/Phase III clinical trials, and 33 out of the 40 Phase III clinical trials have not yet reported results uploaded on the ClinicalTrials.gov database, and thus we cannot assess them. In all the Phase II and Phase II/Phase III clinical trials and in 39 of the 40 Phase III clinical trials participants of both sexes participated; in the one remaining Phase III clinical trial only men participated.

The average number of participants was 372.47 ( $\pm$  740.60) people. The number of participants ranged from 5 to 4891 people. The box-plot of the number of participants after removing 3 clinical trials with an enrollment of more than 2000 participants, is given in Fig. 1a. The median number of participants was about 120 people. The average duration of the clinical trials was 146.64 ( $\pm$  160.04) days, i.e., 4.33 months. The duration ranged from 15 to 1401 days. The box-plot of the duration of the completed clinical trials, after removing 3 clinical trials with a duration of more than 550 days, is given in Fig. 1b. The median duration was about 3 months. The relation between the number of participants and the duration of the clinical trials is given in Fig. 2. For Phase II and for Phase II/Phase III clinical trials a significant relation was observed (Spearman's  $\rho=0.538$ ,  $p < 0.001$  and Spearman's  $\rho = 0.689$ ,  $p = 0.040$ , respectively).

The majority (82 out of 96) of the clinical trials used a parallel assignment design. Seven clinical trials used a single-group assignment, three used a crossover design, two used a factorial assignment, and two used a sequential design.

Almost half of the clinical trials (49 out of 96) used no masking, i.e., all involved were aware of the treatment. Five clinical trials used single masking; in three clinical trials, the participants were unaware of the treatment, in two clinical trials the outcomes assessor was unaware, while in one clinical trial the investigator was unaware of the treatment. 20 clinical trials used double masking; in 13 clinical trials, the participants and the investigators were unaware, in four clinical trials the participants and the care providers were unaware, while in three clinical trials the participants and the outcomes assessor were unaware of the treatment. Six clinical trials used triple masking; in two of them the participants, the care providers, and the outcomes assessors were unaware, in two the care providers, the investigators, and the outcomes assessor were unaware, in one clinical trial the participants, the care providers, and the investigators were unaware, and in one clinical trial the participants, the investigators, and the outcomes assessors were unaware of the treatment. Finally, in 15 clinical trials, quadruple masking was used, i.e., all involved (participants, care providers, investigators, and outcomes assessors) were unaware of the treatment.

The clinical trials assessed a variety of multiple outcomes/endpoints. The most prevalent was mortality, followed by the presence of side effects and the duration of hospitalization.



**Fig. 1** The box-plots for the number of participants after removing 3 clinical trials with enrollment more than 2000 participants (a) and the clinical trial duration after removing 3 clinical trials with duration more than 550 days (b)

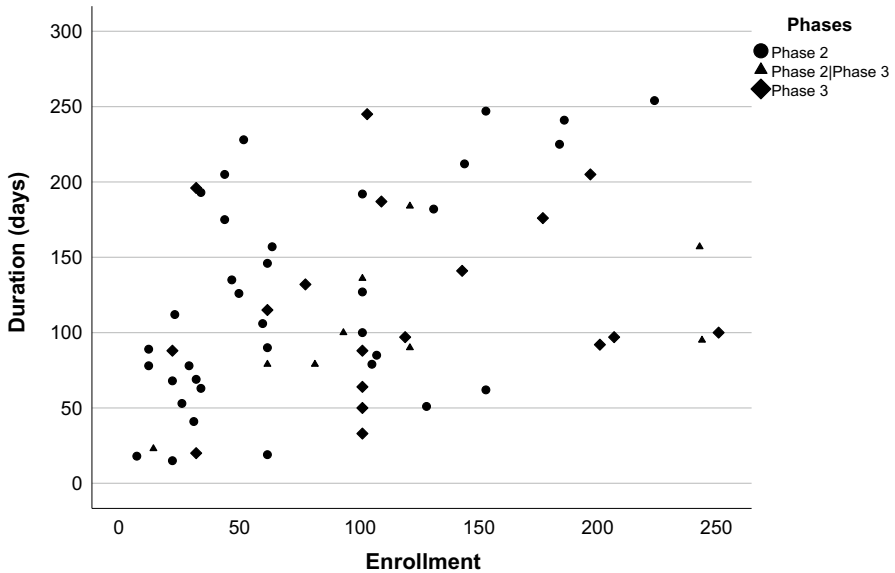


Fig. 2 The relation between the number of participants and the duration of the clinical trials

## 4.2 Analysis Per Phase

The methodological characteristics of the clinical trials per phase are presented in Table 1. As we can observe, the average enrollment of Phase II clinical trials was considerably smaller than the average duration of Phase III clinical trials ( $p < 0.001$ ). The stratified analysis also showed that the 25% of Phase II clinical trials had fewer than 30 participants while the 25% of Phase III clinical trials had fewer than 101 participants. Half of Phase II clinical trials had 60 participants while half of Phase III clinical trials had 294 participants. The 75% of Phase II clinical trials had less than 140 participants while the 75% of Phase III clinical trials had less than 525 participants.

No significant differences in the duration of the clinical trials were revealed among the phases ( $p = 0.949$ ). Moreover, 25% of Phase II clinical trials were completed in about 2 and a half months while the 25% of Phase III clinical trials were completed in about 3 months. Half of Phase II clinical trials were completed in about three and a half months while half of Phase III clinical trials were completed in less than 4 months. The 75% of Phase II clinical trials were completed in about 6 and a half months while the 75% of Phase III clinical trials were completed in about 5 and a half months.

The 80% of Phase II, the 93.7% of Phase II–III, and the 92.5% of Phase III clinical trials used a randomization allocation. There was no significant association between the phase and the allocation of the clinical trials ( $p = 0.065$ ).

33 out of the 40 Phase II clinical trials used a parallel assignment design. The other 7 Phase II clinical trials used a single-group assignment design. The majority of Phase III clinical trials (37 out of 40) also used a parallel assignment design.

**Table 1** The methodological characteristics of the clinical trials per phase

	Phase I ( <i>n</i> = 40)	Phase II–Phase III ( <i>n</i> = 16)	Phase III ( <i>n</i> = 40)	<i>p</i> -value
Enrollment	106.67 (121.423)	430.81 (593.184)	614.93 (1025.590)	< 0.001
Duration (days)	134.70 (93.071)	198.38 (324.377)	137.88 (109.242)	0.949
<i>Allocation</i>				
Non-Randomized	2 (5.0)	1 (6.3)	3 (7.5)	
Randomized	32 (80.0)	15 (93.7)	37 (92.5)	0.063
NA	6 (15.0)	0 (0.0)	0 (0.0)	
<i>Intervention model</i>				
Single-group Assignment	7 (17.5)	0 (0.0)	0 (0.0)	
Parallel assignment	33 (82.5)	12 (75.0)	37 (92.5)	
Sequential assignment	0 (0.0)	2 (12.5)	0 (0.0)	< 0.001
Crossover assignment	0 (0.0)	1 (6.3)	2 (5.0)	
Factorial assignment	0 (0.0)	1 (6.3)	1 (2.5)	
<i>Masking</i>				
None	26 (65.0)	5 (31.3)	18 (45.0)	
Single	0 (0.0)	4 (25.0)	3 (5.0)	
Double	6 (15.0)	2 (12.5)	12 (30.0)	0.027
Triple	2 (5.0)	1 (6.3)	3 (7.5)	
Quadruple	6 (15.0)	4 (25.0)	5 (12.5)	

Enrollment and Duration are presented as mean (standard deviation)

NA not applicable

Two Phase III clinical trials used a crossover design and one used a factorial design. Regarding the Phase II–III clinical trials, 12 of them used a parallel design, two used a sequential design, one used a crossover design, and one used a factorial design. A significant association between the phase and the intervention model emerged ( $p < 0.001$ ).

Regarding masking, the majority of all phases used no masking. A significant association between the phase and the masking emerged ( $p = 0.027$ ).

### 4.3 Analysis Per Intervention Model

In Table 2, the methodological characteristics of the 96 clinical trials per intervention model are presented. Crossover clinical trials and single-group clinical trials had the smallest average sample size (83 and 92, respectively) while the clinical trials with factorial assignment had the larger average sample size. The clinical trials with single-group assignment, sequential assignment, and crossover assignment had the smallest duration (about 3 to 3 and a half months on average). The clinical trials with a factorial design had the largest duration (about 14 months on average).

All seven clinical trials with single-group assignment were of Phase II, while the clinical trials with parallel groups were approximately evenly distributed in the



**Table 2** The methodological characteristics of the clinical trials per intervention model

	Single-Group Assignment ( <i>n</i> = 7)	Parallel Assignment ( <i>n</i> = 82)	Sequential Assignment ( <i>n</i> = 2)	Crossover Assignment ( <i>n</i> = 3)	Factorial Assignment ( <i>n</i> = 2)	<i>p</i> -value
Enrollment	91.14 (178.65)	395.48 (776.97)	291.00 (69.30)	82.67 (84.32)	930.00 (1230.37)	0.036
Duration (days)	100.29 (61.88)	146.05 (159)	107.50 (70.00)	104.67 (77.02)	435.00 (393.15)	0.367
<i>Phases</i>						
Phase II	7 (100.0)	33 (40.2)	0 (0.0)	0 (0.0)	0 (0.0)	
Phase II- Phase III	0 (0.0)	12 (14.6)	2 (100.0)	1 (33.7)	1 (50.0)	< 0.001
Phase III	0 (0.0)	37 (45.1)	0 (0.0)	2 (66.7)	1 (50.0)	
<i>Allocation</i>						
Non-Rand- omized	1 (14.3)	4 (4.9)	0 (0.0)	1 (33.3)	0 (0.0)	
Randomized	0 (0.0)	78 (95.1)	2 (100.0)	2 (66.7)	2 (100.0)	< 0.001
NA	6 (85.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
<i>Masking</i>						
None	7 (100.0)	39 (47.6)	1 (50.0)	2 (66.7)	0 (0.0)	
Single	0 (0.0)	5 (6.1)	0 (0.0)	0 (0.0)	1 (50.0)	
Double	0 (0.0)	19 (23.2)	0 (0.0)	1 (33.7)	0 (0.0)	0.158
Triple	0 (0.0)	5 (6.1)	0 (0.0)	0 (0.0)	1 (50.0)	
Quadruple	0 (0.0)	14 (17.1)	1 (50.0)	0 (0.0)	0 (0.0)	

Enrollment and Duration are presented as mean (standard deviation)

NA not applicable

two phases. The more complex designs were used for Phase III or a combination of Phase II and Phase III clinical trials. The majority of all clinical trials, except those with a single-group assignment, used randomization to administer the treatments to the patients. Two out of the three crossover clinical trials used no blinding. This was also the case in about half of the clinical trials with the parallel and sequential assignments (Table 2).

#### 4.4 Risk of Bias

Figure 3 presents the Cochrane bias risk assessment results. As it is presented the quality of the clinical trials methodology is somehow uncertain. The majority of the clinical trials reported randomization (selection bias), while only six trials had a high risk of bias in the randomization; six clinical trials did not mention such information. The risk of performance bias was approximately equal; almost half of the clinical trials had a low risk of performance bias. Regarding detection bias, about 74% had a high risk of such a bias. The risk of attrition bias, reporting bias, or another bias was unclear, as none of the clinical trials provided such information.

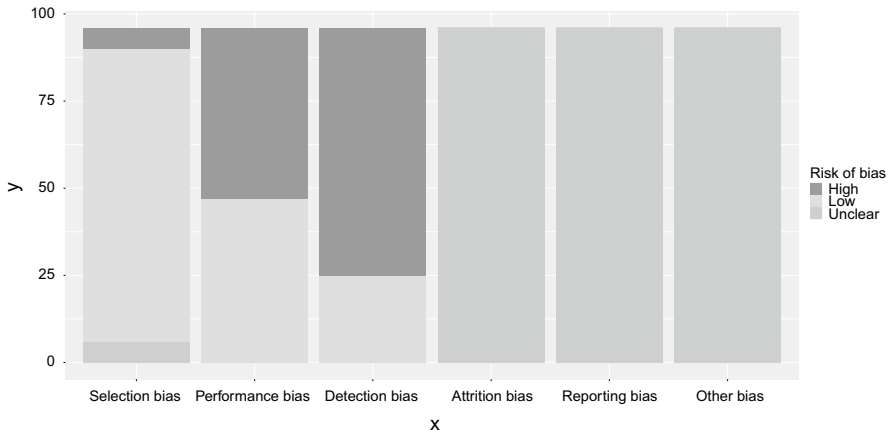


Fig. 3 Risk of bias assessment

### 5 Discussion

During the first year of the pandemic, 96 clinical trials on COVID-19 had been completed. Although the ClinicalTrials.gov database has a number of limitations, it is the most comprehensive resource for information on clinical trials. The retrieved trials showed several differences in their methodological characteristics even within the various phases.

An important feature of clinical trials that affects the validity of their results is the sample size. Our study showed that the 25% of Phase II clinical trials had less than 30 participants while the 25% of Phase III clinical trials had less than 101 participants. For both phases of the clinical trials, these sizes are small enough. Phase III clinical trials had approximately six times the sample size of Phase II clinical trials, which is reasonable. One would expect the clinical trials using a more complex design to be larger in size as well. However, this was only the case for factorial design. Clinical trials with a crossover design had enrolled on average 83 participants; the least in comparison to all other intervention models. Freiman et al. [21] highlighted the significant role that the sample size plays in the design and interpretation of clinical trials.

The majority of the clinical trials, regardless of phase and design, were randomized, which is important for the reliability of the trials. As Kang et al. [22] mentioned, the implementation of randomization increases both the power and validity of the results and improves the quality of the provided care.

The dominant design, regardless of phase, was the parallel assignment. This is reasonable to some extent since the researchers are trying to quickly develop an effective therapy for a disease that so far seems to be very resistant. However, more complex designs, such as factorial or cross-over designs, could improve the reliability of clinical trials' results. It is encouraging that some clinical trials used such designs. Although there is no perfect study design for every test situation,

Nair [23] provided a general algorithm for the choice of the appropriate study design for several test situations.

A negative point of the completed clinical trials on COVID-19 is that almost all Phase II clinical trials and almost half of the Phase III trials used no blinding. As Schulz and Grimes [24] mentioned, blinding usually reduces information bias, on the one hand, and improves compliance and retention of the participants, on the other hand. Unfortunately, a significant number of studies do not contain proper reporting on this information. The fact that the participants knew the treatment they were given may have affected the results. It would be beneficial for the reliability of the results of the clinical trials at least for participants and care providers to be unaware of the treatment.

Many times, researchers are paying more attention to quick results than the correct design of the clinical trials. However, the duration of a clinical trial is affected by several factors such as the design, the endpoints, the sample size, and the sampling methods [25]. Several authors have dealt with the minimization of the duration of clinical trials by proposing appropriate stopping rules [26–28]. For the present study, it was not possible to study the factors that affected the duration of the retrieved clinical trials as this information is not contained in the ClinicalTrials.gov database.

Due to the nature of the study, some limitations exist. The results derived are representative only of the clinical trials registered in the ClinicalTrials.gov database; some trials may not be registered in the database. Moreover, given that the characteristics are submitted by sponsors or investigators, may be subject to error. Due to missing values (not entered into the database), it was not possible to perform more complex analyses (e.g., multivariate analysis). Additional characteristics of the clinical trials that could have been recorded are whether a sample size calculation was made and if so in what way, the sampling methods, which statistical techniques were used to analyze the data, etc.

## 6 Conclusion

A total of 96 clinical trials on COVID-19 have been completed until the time of the database search. Although the registered trials contain significant heterogeneity in their methodological features, the majority of them follow a proper methodological design. This means that the scientific community is ready to quickly and effectively deal with emergency situations such as the appearance of the coronavirus at the end of 2019. However, we should be very careful when reading the results of clinical trials and always interpret them taking into account their methodological characteristics.

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## Declarations

**Conflict of interest** The authors have no competing interests to declare that are relevant to the content of this article.

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