RESEARCH ARTICLE

REVISED Clinical trials for treatment or prevention of COVID-19. A review of Clinicaltrials.gov. [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has rapidly progressed into the worst pandemic in recent years. There are currently no approved therapies to treat the disease. Several clinical trials are being conducted to evaluate therapeutic approaches.

Methods: We conducted a cross-sectional descriptive study to examine the main characteristics of COVID-19-related clinical interventional trials registered with ClinicalTrials.gov from January to March 27th, 2020. .

Results: We included 519 trials, 57.6% were phase II or III, open-label and randomized trials. Disease treatment was evaluated in 75.5% of trials, while prevention was evaluated in 12.1%. A total of 243 trials were listed as recruiting, and 42.4% were not yet recruiting. Approximately 20% of the analyzed trials are investigating antimalarial agents, while 10.2% are studying the use of convalescent plasma to treat the disease. Antiretrovirals, monoclonal antibodies, the use of stem cells, nitric oxide gases and vaccines are the most commonly evaluated therapies. As of the publication of this review, none of the clinical trials had uploaded results.

Conclusions: ClinicalTrials.gov is an important database that contains ongoing research trials on COVID-19. This study quantifies the outcomes of COVID-19-related clinical trials. More than 500 studies have been analyzed finding that most of these studies are interventional clinical trials Phase II or III evaluating drugs or biological agents for the prevention or treating COVID-19.

Keywords

COVID-19, clinical trials, coronavirus, SARS-CoV2

Open Peer Review

Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the **Emerging Diseases and Outbreaks** gateway.

This article is included in the **Coronavirus** collection.

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Author roles: **Fors M:** Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **González P:** Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

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REVISED Amendments from Version 1

We added reviewers main observations. In the methods section we eliminated the paragraph regarding the creation of new variables from the extracted data according to the reviewer comments. We also clarified one inclusion criteria regarding dates. We added initials of the names of the independent reviewers in brackets. We also added a phrase regarding funding sources of the trials according to clinicaltrials.gov definitions. We changed conclusions of the manuscript. We include two new references.

Any further responses from the reviewers can be found at the end of the article

Introduction

The world is currently experiencing a general crisis regarding the healthcare system. SARS-CoV-2 has become a pandemic, and it has affected over 150 countries in a matter of weeks. The inability of many public health systems to address the spread of this disease has become notorious in many countries where the number of individuals with the disease and the number of deaths increase every day.

Coronavirus disease 2019 (COVID-19) is caused by the SARS-CoV-2 betacoronavirus. COVID-19 shares 79% sequence identity with SARS-CoV, the virus that caused a major outbreak in 2002–2003¹.

The clinical characteristics of COVID-19 include pyrexia, radiological signs of acute respiratory distress, reduced or normal white blood cells, lymphopenia, and a failure to resolve complications (e.g., secondary bacterial infections such as bacterial pneumonia) after 3 to 5 days of antibiotic treatment².

The presence of contradictory information on possible treatments for this disease, some of which lacks a scientific foundation, has generated irresponsible actions regarding approached to treat COVID-19³.

Randomized controlled trials (RCTs) are the gold standard design for evaluating the efficacy and safety of clinical interventions and are valued for their statistical rigor and low levels of bias⁴.

Regulatory agencies are also contributing to the response to the coronavirus outbreak by providing general recommendations on how to use certain medicines that are still under investigation and guidance on measures that should be taken to stop the spread of the disease⁵.

[ClinicalTrials.gov](https://clinicaltrials.gov) is a clinical trials registry that provides patients, family, health care professionals, investigators, and the general public with information about clinical studies on a wide range of diseases and conditions. This site is supported by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) of the United States of America⁶.

This database provides a public list of initiated, ongoing, and completed clinical trials, and it is considered a source of summary result information to complement the medical literature. It is the world's largest clinical trial registry, and it is publicly available and accessible to all citizens⁷.

How should COVID-19 be treated and what treatment options should be made available? Well-designed clinical trials are the answer to this question since they are the only type of study that is capable of assessing the efficacy and safety of new therapeutic approaches for any disease^{8,9}.

In 2005, the [International Committee of Medical Journal Editors](https://www.icmje.org/) (ICMJE) required that intervention trials be registered prior to the enrollment of the first subject as a prerequisite for publication in scientific journals. The registration of all clinical trials in any of the available public databases guarantees the transparency of research.

The numbers of cases and deaths caused by this pandemic are increasing continuously, demonstrating the need to identify therapeutic options for the disease. Drug repurposing may prove to be the best strategy for the quick development of novel therapeutic options¹⁰.

There are several drugs that are being evaluated, and some of the trials have yet to be initiated. Infected persons need to be treated with these drugs, but it is also necessary to determine the efficacy and safety profile of the therapies that are being used. There is a need to increase knowledge about the disease and enhance research efforts to find a cure for COVID-19, which will provide a scientific basis to make important decisions in health systems worldwide.

In this cross-sectional study, we aimed to examine the main characteristics of COVID-19-related clinical trials that were registered in [ClinicalTrials.gov](https://clinicaltrials.gov) from January to March 27th, 2020.

Methods

Study design

This is a cross-sectional analysis of all interventional studies that were registered on [ClinicalTrials.gov](https://clinicaltrials.gov) from January to March 27th, 2020. The database was downloaded on May 15th, 2020.

Methods

A combination of search terms was used to retrieve interventional trials that examined COVID-19 ("coronavirus," "SARS- CoV-2", COVID-19). All trials were reviewed by two independent reviewers (MF and PG). Data on the design, masking, randomization, primary purpose, interventions, sample size grouping, type of therapeutic approaches and location of the included studies were extracted by the two reviewers (MF and PG) manually. Information about recruitment status, phases of the trials, and funding sources were used the same way the database was established. The search was restricted to interventional trials. The reviewers MF and PG extracted the data and checked each other's work for accuracy. Disagreements between the two reviewers were settled by consensus.

Inclusion criteria

1. Trials investigating an intervention(s) on humans related to COVID-19
2. Study in any phase
3. Registered or published in ClinicalTrials.gov prior to March 27th, 2020.

Exclusion criteria

1. None

Variables

Most of the information regarding the design of the studies was in the same column in the original downloaded database; for the purposes of our analysis, elements of the design were separated into different variables within the database, and no additional form was used. We extracted the information in the same way as it is reflected in ClinicalTrials.gov: (see [ClinicalTrials.gov data elements definitions](#)):

Clinical trials were classified according to phase (I, I/II, III, II/III, III, or IV), type of intervention models (single group assignment, parallel assignment, and sequential assignment), type of allocation (randomized allocation, nonrandomized and not applicable in case there was only one group of treatment), and type of masking (open label, single-blind masking, double-blind masking, triple-blind masking and quadruple-blind masking).

Other characteristics of interest included primary purpose (basic science, treatment, supportive care, screening, diagnosis, prevention, health research services and others) and intervention type (drug, biological, behavioral, medical devices, diagnostic or other).

Recruitment status was also recorded (not yet recruiting: the study has not started recruiting participants; recruiting: the study is currently recruiting participants; not recruiting: the study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled; terminated: the study has stopped early and will not start again; completed: the study has ended normally, and participants are no longer being examined or treated; withdrawn: the study stopped early, before enrolling its first participant; or unknown: a study on ClinicalTrials.gov whose last known status was recruiting, not yet recruiting, or active, not recruiting but that has passed its completion date and the status has not been verified within the past 2 years),

We included trials with participants of all ages and genders. We classified trials according to the estimated number of participants and categorized them as follows: up to 100, 101–500, 501–1000, + 1000 participants. We used the traditional development phases approach for the size of trials.

We also recorded the funding source for the trial. This describes the organization that provides funding or support for a clinical study. This support may include activities related to funding, design, implementation, data analysis, or reporting. Organizations listed as sponsors and collaborators for a study are considered the funders of the study. Classification of funding sources was the same used by clinicaltrial.gov.

Statistical analysis

Data were extracted directly from the ClinicalTrials.gov database, which contains information for all registry records, and we downloaded a file in comma-separated values (.csv) format (see underlying data: (<https://osf.io/28jh7/>)¹¹). We performed a descriptive analysis of COVID-19-related clinical trials registered in the database downloaded on May 15th, 2020.

Descriptive statistics were used to summarize the trial characteristics: categorical variables are reported as frequencies and percentages, while enrollment rate is reported as the median and IQR. All the data were analyzed using SPSS 24.0.

Results

Characteristics of COVID-19 trials

Among the 339,723 studies registered in the database, 829 were COVID-19-related trials, 519 of which were interventional studies (62.6%), making them eligible for inclusion in our study ([Figure 1](#)).

Phase II and Phase III studies were the most common (30.1% and 18.1%, respectively). Parallel assignment design was the most common study design (77.8%). Most clinical trials were open-label (59.7%) and randomized (75.5%). Disease treatment trials accounted for 75.5% of the eligible trials. Approximately 60% of the studies were evaluating drugs ([Table 1¹¹](#)).

Funding/status of the studies/age of participants

The funding characteristics for all interventional trials are displayed in [Table 2¹¹](#). The most common source of funding was the pharmaceutical industry (12.3%).

As of May 2020, 243 of 519 trials were recruiting subjects, while 42.4% had their status as “not yet recruiting”. Only ten of the trials were completed, and 25 were enrolling by invitation. A total of 0.6% were suspended trials, and 1.0% were withdrawn trials. Most of the studies (87.1%) included subjects who were 18 years and older ([Table 2¹¹](#)).

Starting date

The median number of trials registered over time was 58 trials per month from January to April 2020. [Figure 2](#) shows the increasing rate of trials posted on this website. During the first days of May, the number of trials registered was 128. Most of the trials found in this review are scheduled to end in 2020.

Figure 1. Flowchart of the review.

Table 1. Main attributes of COVID-19 trials.

	No.	%
Phase		
Early Phase 1	8	1.5
Phase 1	22	4.2
Phase 1/Phase 2	24	4.6
Phase 2	156	30.1
Phase 2/Phase 3	49	9.4
Phase 3	94	18.1
Phase 4	31	5.9
Not applicable	135	26.0
Design		
Parallel assignment	404	77.8
Single group assignment	85	16.4
Sequential assignment	20	3.9
Factorial	3	.6
Crossover	7	1.3
Masking		
Open-label	310	59.7
Single-blind	47	9.1
Double-blind	49	9.4
Triple-blind	34	6.6
Quadruple-blind	79	15.2

	No.	%
Randomization		
Randomized	392	75.5
Nonrandomized	53	10.2
Not applicable	74	14.3
Primary Purpose		
Treatment	392	75.5
Prevention	63	12.1
Supportive care	20	3.9
Diagnostic	14	2.7
Health services research	8	1.5
Screening	4	0.8
Basic science	4	0.8
Other	14	2.7
Intervention		
Drug	311	59.9
Biological	79	15.2
Diagnostic test	15	2.9
Behavioral	16	3.1
Device	24	4.6
Procedure	11	2.1
Dietary supplement	8	1.5
Other	55	10.7
Total	519	100.0

Table 2. Clinical trials by funding sources, recruitment status and age.

Funding sources	No.	%
Industry	64	12.3
Industry/Other	21	4.0
Other/Industry	29	5.6
Other/NIH	5	1.0
NIH	4	0.8
U.S. Fed	1	0.2
U.S. Fed/Other	1	0.2
Other	394	75.9
Recruitment status		
Not yet recruiting	220	42.4
Recruiting	243	46.8
Active, not recruiting	12	2.3
Enrolling by invitation	25	4.8
Completed	10	1.9
Suspended	3	0.6
Terminated	1	0.2
Withdrawn	5	1.0
Age		
Adults and older adults	452	87.1
Adults	23	4.4
Children, adults, and older adults	36	6.9
Older adults	5	1.0
Children	2	0.4
Children and adults	1	0.2
Total	519	100.0

Sample size (enrollment)

To assess the enrollment of participants in clinical trials, the authors recategorized this variable into four groups. It was observed that 42.6% of trials had up to 100 participants, and 39.5% had 101–500 participants (Figure 3). The median enrollment was 144 participants (IQR 350).

Type of therapeutic approaches

Among the included studies, 22.8% were investigating antimalarial agents, while 10.8% were investigating the use of convalescent plasma. Other therapeutics under evaluation included new vaccines (2.6%) as well as monoclonal antibodies, interferons and antiretrovirals (Table 3¹¹).

Gender

Among the included studies, 98.8% comprised both sexes, while 1.2% recruited only female participants.

Study results

None of the included trials have posted any results.

Discussion

This study provides a review of COVID-19-related clinical trials registered with ClinicalTrials.gov during the first five months of 2020. We examine the characteristics of the trials, including their design, location, funding characteristics, recruitment status, age of participants, gender of participants and study sample size. A living protocol has been published and the intention is to examine COVID-19-related trials registered in the WHO International Clinical Trials Registry Platform¹².

Phase II and Phase III were the most common study phases. Almost all the included trials included participants of both sexes, the minority was in only in women but not related to specific populations; most of them included adults and older adults and aged between 18 and 99 years old.

More than 75% of the studies we analyzed were randomized trials, which are considered the gold standard for evaluating

Figure 2. Rate of registered clinical trials according to months of the year in 2020.

Figure 3. Enrollment by sample size groups.

Table 3. Type of therapeutic approaches. Drugs and biological agents.

Approaches	No.	%
Chloroquine or hydroxychloroquine	89	22.8
Convalescent plasma	42	10.8
Lopinavir	9	2.3
Vaccines	10	2.6
Nitric oxide gas (iNO)	9	2.3
Tocilizumab	8	2.1
Interferons	7	1.8
Sarilumab	7	1.8
Remdesivir	6	1.5
Colchicine	6	1.5
Azithromycin	5	1.3
Favipiravir	5	1.3
Stem cells	5	1.3
Ivermectin	3	0.8
Aspirin	3	0.8
Losartan	3	0.8
Ruxolitinib	3	0.8
Other	148	43.6
Total	390	100.0

most likely due to the efforts of many countries to combat this novel disease for which there is currently no treatment. The response to the COVID-19 pandemic from the community, particularly from researchers, has been excellent, but it is necessary to ensure the rights, safety and wellbeing of subjects. Well-designed clinical trials are important for guaranteeing these rights.

A large proportion of studies (42.6%) enrolled 100 or fewer patients, but these studies are in the early phases of development, and thus, we are not concerned that these studies are underpowered or have a high risk of type II errors (signification level), which would lead to inappropriate conclusions regarding the effectiveness of a therapeutic approach^{13,14}.

Overall, most trials focused on the treatment of the disease. This indicates that the possible therapeutic benefits of these interventions include reducing the number of fatal events due to the disease.

As indicated by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) has not approved any drugs for treating COVID-19 that have demonstrated an adequate safety profile and adequate efficacy in randomized clinical trials with control groups¹⁵. According to the FDA, therapies that are under investigation to treat COVID-19 should only be examined in randomized controlled trials¹⁵.

Among the included studies, approximately 22% are evaluating antimalarial drugs such as chloroquine and hydroxychloroquine. Available evidence regarding the use of chloroquine in COVID-19 patients is limited, so there is still very low confidence in its efficacy for treating COVID-19. The use of chloroquine in the treatment of SARS-CoV-2 should be analyzed in light of both its promise and the potential adverse

the efficacy and safety profile of any new treatment or for a new medical indication. The number of registered trials was high,

effects that have been observed in past endeavors to treat intense viral illnesses with chloroquine¹⁶.

A systematic review of the use of chloroquine concluded that there is sufficient evidence of its effectiveness and safety for other indications, which justifies the clinical research on the use of chloroquine to treat patients with COVID-19¹⁷.

Currently, the use of the Monitored Emergency Use of Unregistered Interventions (MEURI) framework or the ethical approval of clinical trials are of vital importance, as stated by the World Health Organization^{17,18}.

We found that the second most commonly used treatment was convalescent plasma, which is examined in 10.3% of the included studies. Using plasma for convalescent patients has been successfully used for the treatment of several viral diseases during different outbreaks, such as the 2003 SARS-CoV-1 epidemic, the 2009–2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic¹⁹. Patients accepting this treatment showed benefits approximately 1 week later, suggesting that high titer levels can be used to effectively neutralize the virus, avoid inflammatory responses and improve symptomatology without severe adverse events²⁰. Information from China has shown that this therapy brings clinical and radiological improvement, decreases viral loads and increases survival times²¹.

Several studies have evaluated multiple drugs with *in vitro* antiviral activity against SARS-CoV-2 and/or immunomodulatory effects that may have clinical benefit. We found that the use of lopinavir combined with ritonavir in the majority of cases was very frequent. The combination of these two drugs and other antiviral agents in the early stages of COVID-19 infection might hold promise for treating COVID-19¹⁷.

Favipiravir was evaluated in 1.3% of the registered trials. This drug is considered a broad-spectrum antiviral that shows promise in the treatment of influenza virus infections, particularly due to the apparent lack resistant mutations against the drug in cell culture or animal studies²².

Remdesivir has also demonstrated its efficacy in inhibiting coronaviruses such as SARS-CoV and MERS-CoV *in vitro*²³. The use of remdesivir has been shown to limit the mortality rate of seriously ill patients needing invasive ventilation and patients who did not need invasive ventilation by 18% and 5%, respectively¹⁷.

The World Health Organization (WHO), the Surviving Sepsis Campaign Guide and the CDC have stated that there is no current evidence to recommend a specific antiviral treatment for patients with confirmed COVID-19, and such evidence can only derive from a controlled clinical trial^{18,24}.

In a study of available scientific information, a group of scientists from Universidad Nacional de La Plata, Argentina, concluded that no studies have provided high-quality evidence for the use of hydroxychloroquine, chloroquine, or lopinavir/ritonavir to treat patients with COVID-19²⁵.

Regarding the use of nitric oxide, The Society of Critical Care Medicine recommends against the routine use of iNO in patients with COVID-19-induced pneumonia. Instead, they suggest the use of this treatment only in mechanically ventilated patients with severe ARDS and hypoxemia despite other rescue strategies²⁴.

There are also a few studies that are evaluating vaccines (2.6%); additionally, there are many pharmaceutical companies developing new vaccines, but many of these evaluations are still in the preclinical stages²⁶.

There are challenges in conducting clinical research on COVID-19, and these challenges are impacting the health systems around the world. There is good clinical guidance²⁷ on how sponsors should adjust the management of clinical trials and participants during the COVID-19 pandemic. These guidelines must be followed to ensure that clinical trials are performed according national and international standards during this pandemic.

Strengths

This is a descriptive assessment of the current information regarding COVID-19 clinical trials registered in the ClinicalTrials.gov registry until March 2020. This database is updated frequently, is very user-friendly and provides transparency regarding the type, design, distribution, and funding of clinical trials.

Limitations

This study has some limitations. ClinicalTrials.gov does not include all the COVID-19 clinical trials registered and performed around the world. This study focuses on only one database; ClinicalTrials.gov is certainly one of the most important sources of information, but many others also provide valuable information. WHO's ICTRP is not very friendly database for quantitative analysis that is why is was not explored to describe clinical trials that are registered in this platform.

Conclusions

The efficacy and safety profile of many different therapeutic measures for patients infected by COVID-19 are being investigated. More than 500 studies have been registered within ClinicalTrials.gov. Most of these studies are interventional clinical trials evaluating drugs or biological agents. These trials have already started and are evaluating different therapeutic approaches for COVID-19 treatment. It is necessary to discover new classes of medicines.

Data availability

Underlying data

Open Science Framework: Clinical trials characteristics for treatment of COVID-19. <https://doi.org/10.17605/OSF.IO/27QCP>¹¹

This project contains the following underlying data:

- SearchResultsCOVID.csv (Extracted data from ClinicalTrials.gov)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Acknowledgments

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References

- Zhou P, Yang XL, Wang XG, *et al.*: **Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin.** *bioRxiv*. 2020.
[Publisher Full Text](#)
- Lake MA: **What we know so far: COVID-19 current clinical knowledge and research.** *Clin Med (Lond)*. 2020; **20**(2): 124–127.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Osuchowski MF, Aletti F, Cavaillon JM, *et al.*: **SARS-CoV-2/COVID-19: Evolving Reality, Global Response, Knowledge Gaps and Opportunities.** *Shock*. 2020.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Saturni S, Bellini F, Braido F, *et al.*: **Randomized Controlled Trials and real life studies. Approaches and methodologies: a clinical point of view.** *Pulm Pharmacol Ther*. 2014; **27**(2): 129–138.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Katz E: **How Federal Agencies Are Responding to the New Coronavirus Outbreak.** Retrieved. 2020. (2020, February 25).
[Reference Source](#)
- ClinicalTrials.gov. 2020.
[Reference Source](#)
- Zarin DA, Tse T: **Medicine. Moving toward transparency of clinical trials.** *Science*. 2008; **3**(19): 1340–1342.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19>
- <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-april-1-2020>
- Senanayake SL: **Drug repurposing strategies for COVID-19.** *Future Drug Discov*. 2020; fdd-2020–0010.
[Publisher Full Text](#) | [Free Full Text](#)
- Fors M: **Clinical trials characteristics for treatment of COVID-19.** 2020.
[Reference Source](#)
- Maguire BJ, Guérin PJ: **A living systematic review protocol for COVID-19 clinical trial registrations [version 1; peer review: 2 approved].** *Wellcome Open Res*. 2020; **5**: 60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kimmel SE, Califf RM, Dean NE, *et al.*: **COVID-19 Clinical Trials: A Teachable Moment for Improving Our Research Infrastructure and Relevance.** *Ann Intern Med*. 2020; **173**(8): 652–653.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bauchner H, Fontanarosa PB: **Randomized Clinical Trials and COVID-19: Managing Expectations.** *JAMA*. 2020; **323**(22): 2262–2263.
[PubMed Abstract](#) | [Publisher Full Text](#)
- CDC: **Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19).**
[Reference Source](#)
- Touret F, de Lamballerie X: **Of chloroquine and COVID-19.** *Antiviral Res*. 2020; **177**: 104762.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Cortegiani A, Ingoglia G, Ippolito M, *et al.*: **A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19.** *J Crit Care*. 2020; **57**: 279–283.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- WHO: **Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance V 1.2.** 2020.
[Reference Source](#)
- Zhang J, Xie B, Hashimoto K: **Current status of potential therapeutic candidates for the COVID-19 crisis.** *Brain Behav Immun*. 2020; **87**: 59–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Roback JD, Guarner J: **Convalescent plasma to treat COVID-19: possibilities and challenges.** *JAMA*. 2020; **323**(16): 1561–1562.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kai D, Liu B, Li C, *et al.*: **Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients.** *Proc Natl Acad Sci U S A*. 2020; **117**(17): 9490–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Goldhill DH, Te Velhuis AJW, Fletcher RA, *et al.*: **The mechanism of resistance to favipiravir in influenza.** *Proc Natl Acad Sci U S A*. 2018; **115**(45): 11613–11618.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sheahan TP, Sims AC, Graham RL, *et al.*: **Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses.** *Sci Transl Med*. 2017; **9**(396): eaal3653.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Walhazzani W, Möller MH, Arabi YM, *et al.*: **Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19).** *Intensive Care Med*. 2020; **46**(5): 854–887.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chloroquine, hydroxychloroquine, lopinavir / ritonavir, for the treatment of COVID-19 infection. CUFAR Rapid Review Report, March 29.
[Reference Source](#)
- Market watch. 2020.
[Reference Source](#)
- EMA: **Guidance on the management of clinical trials during the COVID-19 (coronavirus)pandemic.**
[Reference Source](#)

Open Peer Review

Current Peer Review Status: ? ✓

Version 2

Reviewer Report 24 June 2021

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Ana Marusic

Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia

It is not clear how the authors responded to individual comments. I expected to see their responses to my specific comments and not a general list of the changes made. These changes are described in a general sense, and not really clear.

My specific comments:

1. The article presents a nice study of the trials on COVID-19 registered in CT.gov. The sample includes the trials registered from January to March 2020. This time frame is interesting as it presents the beginning of the pandemic, which was proclaimed at the end of March. It seems that the data presented in the paper were downloaded in May 2020. One of the main findings in the study is that not many trials were completed at that time and that the results were not registered (the authors do not mention reporting of results in journals or preprints). The authors should provide the rationale for not following the trials from January to March 2020 in time or extent their analysis in time to show the fate of the cohort of trials from a snippet of time of COVID-19 pandemic.
2. I do not understand the Discussion section on current findings on interventions that were tested in the registered trials at the beginning of the pandemic. It would be more interesting, as I said in the above comments, that the authors presented the findings of the studies, and then compared them to the current existing evidence (which changes continually, both from new trials and real world data).
3. The conclusions are not clear so the whole point of the study and its message are not clear.
4. The language of the manuscript needs improvement.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Trial registration and transparency, research integrity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 June 2021

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Andrea Cortegiani

¹ Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.), University of Palermo, Palermo, Italy

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I have no further comments

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Intensive care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 17 Jun 2021

Martha Fors, Universidad de las Américas, Quito, Quito, Ecuador

Thank you very much for the comments and for the time you expended in reviewing the manuscript.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 19 August 2020

<https://doi.org/10.5256/f1000research.27128.r68401>

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The authors submitted an interesting research article, reporting an analysis of the ongoing clinical trials on interventions for COVID-19.

I have some concerns and some suggestions for the authors.

Below, my specific comments by section.

Title:

1. The title is not clear in its current form. I suggest avoiding the use of questions and clearly expressing the design of the study. I see no need to add the date of the last update in the title and probably the phrase needs language editing.

Abstract:

1. I suggest avoiding the use of “most of”. The authors should report specific data.
2. Conclusions should focus on the key messages of the paper.

Methods:

1. When saying “All trials were reviewed by two independent reviewers”, please enter the initials of the reviewers in brackets.
2. The phrase “Using this search strategy, 519 trials were identified.” should be moved down to the results section.
3. The phrase “since the information extracted directly from the database was not suitable for statistical analysis and because it was necessary to create new variables with the extracted information” is not very clear. If not useful for the reproducibility of the methods, the authors may also consider to remove it.
4. The authors say that “Descriptive statistics were used to summarize the trial characteristics: categorical variables are reported as frequencies and percentages, while continuous variables are reported as the mean and standard deviation. All the data were analyzed using SPSS 24.0”. Was the normality of data distribution evaluated before selecting mean and SD as appropriate?
5. The timing of the study is unclear. The introduction says “we aimed to examine the main characteristics of COVID-19-related clinical trials that were registered in ClinicalTrials.gov prior to March 27th, 2020”. In the methods section, it is then said that “The database was

downloaded on May 15th, 2020" and finally the results say "During the first days of May, the number of trials registered was 128". Please clarify any timing restriction used as exclusion criteria and the exact date of data collection.

Results:

1. The authors say "the approximately 339,723 studies". Is the total number of registered studies available? If so, the exact number should be used, without approximations.
2. According to Figure 1, the number 339,723 seems to be the result of the authors' search query. This is in contrast with what stated in the main text. Please clarify.
3. Looking at table 2, it is not clear what difference exists between "Industry", "Industry/Other", "Other/Industry".
4. Please provide IQR when reporting medians (e.g. "The median enrollment was 144 participants").

Discussion:

1. The authors say that "Another review has examined COVID-19-related trials registered in the WHO International Clinical Trials Registry Platform, and the first results have already been published" but the reference regards the protocol. I suggest to refer to the results, if available as said, and to discuss the similarity and the differences with the present study.
2. The authors say "A large proportion of studies (42.6%) enrolled 100 or fewer patients, but these studies are in the early phases of development, and thus, we are not concerned that these studies are underpowered or have a high risk of type II errors (signification level), which would lead to inappropriate conclusions regarding the effectiveness of a therapeutic approach". This aspect has been largely debated and probably some references may be added to provide a more balanced discussion (e.g. <https://doi.org/10.7326/M20-2959>; <https://doi.org/10.1001/jama.2020.8115>).^{1,2}
3. In the results section the authors say that "Among the included studies, 98.8% comprised both sexes, while 1.2% recruited only female participants". Is this 1.2% related to specific populations (e.g. pregnant patients)? This may be eventually discussed and compared to recently published findings on this population (e.g. <https://doi.org/10.1016/j.bja.2020.05.020> ; <https://doi.org/10.1002/eahr.500060>; [https://doi.org/10.1016/S1473-3099\(20\)30638-1](https://doi.org/10.1016/S1473-3099(20)30638-1))^{3,4,5}, that seems to be understudied.

Conclusions:

1. Conclusions should convey a key message for the readers.
2. Strengths and limitations may be probably moved to the discussion section.

General and Minor Comments:

1. Language editing is strongly suggested to improve the quality of the manuscript.
2. The osf registration (dated 24th June) says that "All studies from January to May 2020 were included". As previously suggested, please verify that the correct timing is reported. The

registration seems to be subsequent to data collection. If so, the authors should not refer to it as underlying data.

3. The reference to the .csv file should be added. The registered project contain a .csv file (<https://osf.io/28jh7/>). If it corresponds to the underlying data of this paper, please add it as a reference.

References

1. Kimmel S, Califf R, Dean N, Goodman S, et al.: COVID-19 Clinical Trials: A Teachable Moment for Improving Our Research Infrastructure and Relevance. *Annals of Internal Medicine*. 2020. [Publisher Full Text](#)
2. Bauchner H, Fontanarosa PB: Randomized Clinical Trials and COVID-19: Managing Expectations. *JAMA*. 2020. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Einav S, Ippolito M, Cortegiani A: Inclusion of pregnant women in clinical trials of COVID-19 therapies: what have we learned?. *British Journal of Anaesthesia*. 2020. [Publisher Full Text](#)
4. Farrell R, Michie M, Pope R: Pregnant Women in Trials of Covid-19: A Critical Time to Consider Ethical Frameworks of Inclusion in Clinical Trials. *Ethics Hum Res*. 2020; **42** (4): 17-23 [PubMed Abstract](#) | [Publisher Full Text](#)
5. Heath P, Le Doare K, Khalil A: Inclusion of pregnant women in COVID-19 vaccine development. *The Lancet Infectious Diseases*. 2020. [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Intensive care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 05 August 2020

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Ana Marusic

Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia

This is an important study describing clinical trials addressing COVID-19. It provides important data on activities undertaken to address the pandemic and it would be interesting to see the update of the study if that is possible in the next version. The study concluded with May 15, and I am sure that the situation with the registration and results changed. For example, there are now 2 studies with results and a total of 2890 registered studies on August 5, 2020 (using Covid19 as a search term).

The authors describe the problem well in the Introduction and address well the methodological approach, which is sound and appropriate.

Agreement between two assessors should be presented (e.g. kappa).

Results are clearly presented and discussed. The discussion section mentions that half of the registered trials were from China, but the data on the geographical locations of the study was not presented. This needs to be corrected. Also, this issue needs to be addressed better in the Limitation section, as it is a pity that the authors did not search WHO's ICTRP portal, which includes CT.gov and many others. Such a search would give a better view of the global effort to combat COVID-19 pandemic.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Trial registration and transparency, research integrity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Aug 2020

Martha Fors, Universidad de las Américas, Quito, Quito, Ecuador

Thank you very much for this report. We will try to keep this information updated and also look for other clinical trials registry as suggested by the reviewer. Martha Fors

Competing Interests: No competing interests

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