




BRIEF REPORT

A snapshot of the ongoing clinical research on COVID-19

[version 1; peer review: 2 approved]

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Abstract

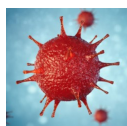
The pandemic of coronavirus disease 2019 (COVID-19) presents an unprecedented challenge to rapidly develop new diagnostic, preventive and therapeutic strategies. Currently, thousands of new COVID-19 patients are quickly enrolled in clinical studies. We aimed to investigate the characteristics of the COVID-19 studies registered in ClinicalTrials.gov and report the extent to which they have incorporated features that are desirable for generating high-quality evidence.

On April 28, 2020, a total of 945 studies on COVID-19 have been registered in ClinicalTrials.gov; 586 studies are interventional (62.0%), the most frequent allocation scheme is the parallel group assignment (437; 74.6%), they are open-label and the most common primary purpose is the research on treatment.

Too many of the ongoing interventional studies have a small expected sample size and may not generate credible evidence at completion. This might lead to a delayed recognition of effective therapies that are urgently needed, and a waste of time and resources. In the COVID-19 pandemic era, it is crucial that the adoption of new diagnostic, preventive and therapeutic strategies is based upon evidence coming from well-designed, adequately powered and carefully conducted clinical trials.



Keywords



SARS-CoV-2, 2019-nCoV, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2, Covid-19





This article is included in the [Disease Outbreaks gateway](#).

Open Peer Review

Reviewer Status  

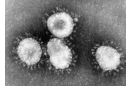
	Invited Reviewers	
	1	2
version 1 18 May 2020	 report	 report

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2 **Ioannis Mamais** , National and Kapodistrian University of Athens, Athens, Greece

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

This article is included in the **Coronavirus**



collection.

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Author roles: **Piovani D:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Pansieri C:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Peyrin-Biroulet L:** Conceptualization, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Danese S:** Conceptualization, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Bonovas S:** Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to rapidly develop new diagnostic, preventive and therapeutic strategies¹. Currently, thousands of new COVID-19 patients present for care every day, and many are quickly enrolled in clinical studies. We aimed to investigate the characteristics of the COVID-19 studies registered in ClinicalTrials.gov², and report the extent to which they have incorporated features that are desirable for generating high-quality evidence.

Methods

We investigated the ClinicalTrials.gov website on April 28, 2020, using the search term: SARS-CoV-2 OR 2019-nCoV OR 2019 novel coronavirus OR severe acute respiratory syndrome coronavirus 2 OR Covid-19. No restrictions were applied. No screening of trials was performed; all results were included regardless of their content.

Stata 15.0 (Stata Corp., College Station, TX, USA) was used for the analysis of study characteristics.

Results

A total of 945 studies on COVID-19 have been registered in ClinicalTrials.gov up to April 29, 2020; 586 studies are interventional (62.0%), and 435 of them (74.2%) are randomized. Among interventional studies, the most frequent allocation scheme is the parallel group assignment (437; 74.6%), followed by single group (111; 18.9%), sequential (18; 3.1%), factorial (9; 1.5%), and cross-over assignment (11; 1.9%). The majority of the clinical trials are open-label (no masking, 338 [57.7%]); however, 57 (9.7%) trials are double-blinded, 41 (7.0%) triple-blinded, 90 (15.4%) quadruple-blinded, and 60 (10.2%) single-blinded. Among observational studies, cohort (222; 64.3%) is the most common study design (Table 1).

Table 1. Characteristics of COVID-19 studies registered in ClinicalTrials.gov (n=945).

Study type	N (%)
Study design (n=945)	
Interventional	586 (62.0)
Observational	345 (36.5)
Expanded access	14 (1.5)
Recruitment status (n=945)	
Recruiting or enrolling by invitation	453 (47.9)
Not yet recruiting	414 (43.8)
Active, not recruiting	24 (2.5)
Completed	27 (2.9)
Withdrawn, terminated or suspended	13 (1.4)
Available	13 (1.4)
Intervention type (n=945)	

Study type	N (%)
Drug	405 (42.9)
Biological (cells, blood sampling, etc)	74 (7.8)
Diagnostic test	60 (6.3)
Device	44 (4.7)
Procedure	18 (1.9)
Behavioral	20 (2.1)
Dietary supplement	9 (1.0)
Other/Unknown	315 (33.3)
Target age (n=945)	
Any age	165 (17.5)
Child (<18 y)	5 (0.5)
Child and adult (<65 y)	8 (0.8)
Adult (18–65 y)	35 (3.7)
Adult and elderly (≥18 y)	720 (76.2)
Elderly (≥66 y)	12 (1.3)
Funding (n=945)	
NIH or federal	13 (1.4)
Industry	82 (8.7)
Industry plus other	63 (6.7)
Other (organizations, universities, individuals)	787 (83.2)
Expected trial size (n=931)	200 (66–504)
0–100	344 (37.0)
101–1000	439 (47.1)
>1000	148 (15.9)
Interventional (n=586) [median (IQR)]	150 (52–420)
Observational (n=345) [median (IQR)]	300 (100–1,000)
Study results (n=945)	
Not available	945 (100)
Interventional studies (n=586)	
Study phase (n=586)	
Phase 0, 1, 1/2	62 (10.6)
Phase 2, 2/3	212 (36.2)
Phase 3, 4	165 (28.1)
Not applicable	147 (25.1)
Model (n=586)	
Parallel assignment	437 (74.6)
Single group assignment	111 (18.9)
Sequential	18 (3.1)
Factorial assignment	9 (1.5)
Crossover assignment	11 (1.9)
Masking (n=586)	

Study type	N (%)
Open label or no masking	338 (57.7)
Single-blind	60 (10.2)
Double-blind	57 (9.7)
Triple-blind	41 (7.0)
Quadruple-blind	90 (15.4)
Study allocation (n=586)	
Randomized	435 (74.2)
Non-randomized	53 (9.1)
Unknown/missing	98 (16.7)
Observational studies (n=345)	
Observational model (n=345)	
Cohort	222 (64.3)
Case-control	34 (9.9)
Case-only	45 (13.0)
Ecologic or community	11 (3.2)
Other	33 (9.6)
Time perspective (n=345)	
Prospective	230 (66.7)
Retrospective	58 (16.8)
Cross-sectional	31 (9.0)
Other	26 (7.5)

Most studies target adult or elderly participants, while 178 (18.8%) enroll children, with only five (0.5%) recruiting exclusively children. Median expected study size is 200 (interquartile range, 66–504), although sample sizes vary from ≤100 (344; 37.0%) to >1,000 individuals (148; 15.9%). Overall, only 27 of 945 studies (2.9%) have completed recruitment, 453 (47.9%) are actively recruiting subjects, while a large number of studies (414; 43.8%) are not yet actively recruiting participants. Most of the studies are conducted in Europe (n=327), North America (n=217, of which 186 in the US), East Asia (n=102), Africa (n=27), and in South America (n=26). No study has reported results yet.

Among the interventional studies, the most common primary purpose is the research on treatment (441; 75.3%), followed by prevention (79; 13.5%), supportive care studies (22; 3.8%), and diagnostic investigations (17; 2.9%). Regarding the drugs under scrutiny, hydroxychloroquine (110; 28.6%), azithromycin (38; 9.9%), lopinavir/ritonavir (24; 6.2%), interferon-α and -β (24; 6.2%), glucocorticoids (22; 5.7%), chloroquine (14; 3.6%), favipiravir (10; 2.6%), remdesivir (8; 2.1%), tocilizumab (21; 5.5%), anti-SARS-CoV-2 immunoglobulins (15; 3.9%) and sarilumab (9; 2.3%) account for the majority of interventional studies. Additional details are featured in [Table 2](#).

Table 2. Characteristics of COVID-19 interventional studies registered in ClinicalTrials.gov (n=586).

Study type	No. (%)
Primary purpose (n=586)	
Treatment	441 (75.3)
Prevention	79 (13.5)
Supportive care	22 (3.8)
Diagnostic	17 (2.9)
Other	13 (2.2)
Screening	5 (0.8)
Basic science	5 (0.8)
Health services research	4 (0.7)
Drugs (n=385)	
<i>Repurposed drugs</i>	
Hydroxychloroquine	110 (28.6)
Azithromycin	38 (9.9)
Lopinavir/Ritonavir	24 (6.2)
Glucocorticoids	22 (5.7)
Interferon-α and -β	24 (6.2)
Chloroquine	14 (3.6)
Nitazoxanide	8 (2.1)
Camostat	4 (1.0)
Oseltamivir	4 (1.0)
Ribavirin	1 (0.3)
<i>Investigational agents</i>	
Favipiravir	10 (2.6)
Remdesivir	8 (2.1)
<i>Adjunctive therapies</i>	
Tocilizumab	21 (5.5)
Anti SARS-CoV-2 immunoglobulins	15 (3.9)
Sarilumab	9 (2.3)

Discussion

Our survey presents the current COVID-19 clinical research landscape. Several hundreds of clinical studies have been initiated all over the globe, and the number is growing. Most interventional studies incorporate randomisation, which is considered the hallmark of high-quality clinical trials³, while more than 40% are blinded.

Studies are being conducted especially in the most affected areas: Europe and US. The number of COVID-19 cases in low

to middle-income countries is still relatively low, also reflecting scarce testing, but is expected to rise in the next period. These countries will need more research on organizational measures, and trials on interventions that are affordable and applicable to those settings⁴.

Most studies focus on adults and elderly, while only few target children, possibly reflecting the observed burden of the disease. Additional effort is needed to ensure that minors are included in COVID-19 clinical research, so that therapeutic decisions are based upon high-quality evidence.

No drug with proven clinical efficacy currently exists for SARS-CoV-2 infection. Despite the absence of solid evidence,

several treatments are being currently used in clinical practice in several countries, with sometimes disastrous consequences⁵. Too many of the ongoing interventional studies have a small expected sample size, and may not generate credible evidence at completion⁴. This might lead to a delayed recognition of effective therapies that are urgently needed, and a waste of time and resources. In the COVID-19 pandemic era, it is crucial that the adoption of new diagnostic, preventive and therapeutic strategies is based upon evidence coming from well-designed, adequately powered and carefully conducted clinical trials.

Data availability

The Clinical Trials website can be accessed here: <https://clinicaltrials.gov/>

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I have read it through, and it seems to be an interesting brief report.

Some comments below:

- 74.2% of those studies are mention as "Randomized" and 40% as blinded, from researchers. Authors of this brief report can "discuss" those numbers and prepare readers that most of those may have a high risk of bias (maybe with no control group, or bias arising from the randomisation process, etc).
- "Additional effort is needed to ensure that minors are included in COVID-19 clinical research, so that therapeutic decisions are based upon high-quality evidence". I am not very sure if it is necessary to discuss this in the brief report

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?

Partly

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

Not applicable

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: Molecular Epidemiology

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.

Reviewer Report 26 May 2020

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This brief report is a survey of the current COVID-19 clinical research landscape. The number of clinical studies on COVID-19 is rapidly growing and it is important the investigation of whether these studies are incorporating features that are desirable for generating high-quality evidence.

This survey performed this investigation and found that too many of the ongoing interventional studies have a small expected sample size. This might lead to delayed recognition of effective therapies and a waste of time and resources. This important evidence should guide the design of any future clinical study on COVID-19 and the decision of any funding body as well as the approval of any bioethics committee. For this reason, I consider this brief report important for the scientific community.

There are a few minor suggestions for the authors:

- Table 1: The presentation of the studies' characteristics will be improved if they are presented separately for interventional and observational studies (particularly for the intervention type and expected study size). In this way, the table will provide more information about the studies' characteristics for each study type (interventional and observational).
- Table 1: It will be useful to report the type of randomization (such as blocking and block size).

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?

Not applicable

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: Epidemiology, Statistics, Research Methods, Public Health

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.

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