Early COVID-19 treatment clinical trials: so much work, so many lost opportunities.

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Systematic Review

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Abstract

Background The Covid-19 pandemic has raged on and heavy clinical research have been promoted worldwide. We aimed to assess the adequacy of treatment clinical trials set forth as early response to COVID-19 pandemic.

Methods First, we performed a systematic review of trial registries. The World Health Organization International Trials Registry Platform and national trial registries were searched for COVID-19 trials through April 19th, 2020. For each record, independent researchers extracted interventions, participants, and methodological characteristics.

Second, we evaluated on September 14th, 2020 the recruitment status and availability of results of COVID-19 treatment trials previously identified.

Results On April 2020, a total of 580 trials evaluating COVID-19 treatment were registered. Reporting quality was poor (core participant information was missing in 24.1% to 92.7%). Between 54.0% to 93.8% of the trials did not plan to include older people and people at higher baseline risk. Most studies were randomised (67.9%), single-centre (58.3%), non-industry funded (81.1%), to be conducted in China (47.6%), with a median duration of 184 days and a median sample size of 100 participants. Core endpoints (mortality, clinical status, and hospitalization length) were planned to be assessed in 5.2% to 13.1% of the trials. Five months later, 66 trials (11.4%) are reported as “Completed”, and only 46 (7.9%) have public results available. 144 of 580 trials (24.8%) are either under the status “Not yet recruiting” or “Suspended”, and 18 (3.1%) trials were prematurely stopped (“Terminated” or “Withdrawn”) The number of completed trials and trials with results are much lower than anticipated, considering the planned follow-up.

Conclusions Our results raise concern regarding the success of the initial global research effort on COVID-19 treatment. The clinical and methodological characteristics of early COVID-19 treatment trials limit their capability to produce clear answers to critical questions in the shortest possible time.

Background

Since December 2019, SARS-CoV-2 has caused a global outbreak of respiratory illness termed coronavirus disease (COVID-19). COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death.[1-3] To date, there are no specific therapeutic agents for COVID-19. Fierce medical research is currently underway, however, there are historical reasons that led us to question if the global research community is maximizing the expected benefit from these efforts.[4] To shed some light to this question we decided to assess the adequacy of treatment clinical trials set forth as early response to COVID-19 pandemic.

Methods

Registry search and trial selection

The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) contains the trial registration datasets provided by 17 clinical trial registries.[5] , It is anticipated that the great majority of ongoing clinical trials are captured and recorded by the databases.[6] We searched the ICTRP for completed and ongoing COVID-19 trial records through April 19th, 2020 using “COVID-19”, “SARS-Cov-2”, “2019-nCoV”, “severe acute respiratory syndrome coronavirus 2”, “2019 novel coronavirus” and “COVID”.

Additionally, we also searched in the three main national clinical trials registries, namely ClinicalTrials.gov, the EU Clinical Trials Register (EUCTR), and the Chinese Clinical Trial Registry (ChiCTR).

We included all interventional trials, irrespective of the intervention under investigation. We excluded duplicate trial entries and trials that did not directly address COVID-19. We did not exclude trials due to incomplete data reporting.

Data extraction

Independent authors selected the trials registered up to April 19th, 2020 and extracted data onto a pre-piloted spreadsheet (supplementary material), classifying each trial as seeking to assess a treatment or prophylactic effect, or both. For each record, we extracted the type of intervention, methodological aspects of the study design and participant characteristics. We assessed whether or not trials plan to include participants with known risk factors for poorer outcomes in COVID-19,[1, 2] namely cancer, chronic obstructive pulmonary disease (COPD), diabetes, heart disease, hypertension, or immunodeficiency.

For each trial identified, we extracted the updated recruitment status on September 14th, 2020, alongside with reasons for trials being prematurely stopped when available. We also assessed the registries for any submitted results or indexed publication on the same date. Additionally, we checked for publications of results of the previous identified trials in WHO's Global Research on Covid-19 Database,[7] Cochrane Covid-19 Study Register,[8] and selected living systematic reviews on covid-19.[9, 10]

Analysis

We conducted statistical analyses using the R software (version 3.6.1). We calculated descriptive statistics to characterize data. We performed statistical comparisons between *post-hoc* defined groups using the Chi-Squared and Kruskal-Wallis tests. We deemed P values of 0.05 statistically significant, with tests being two-sided. We conducted sample size calculations using different baseline scenarios for case fatality rates (CFR) for the control group (2%, 5%, and 10%), as the true CFR is largely unknown[11] and liable to change over time. We considered different possible treatment effects. All sample size calculations considered a significance level of 0.05 and a power of 80%.

Results

We found 693 records of clinical trial protocols (supplementary material), 648 (93.5%) on COVID-19 and 45 (6.5%) on COVID-related conditions (notably pulmonary rehabilitation or exercise and mental health among healthcare workers).

Among COVID-19 trials, 572 (88.3%) evaluate treatment only (table 1), 68 (10.5%) evaluate prophylaxis only, and 8 (1.2%) evaluate both. Our results focus on the 580 trials evaluating COVID-19 treatment.

Quality of reporting

The quality of reporting across the trial registries is globally poor. In trial protocols covering COVID-19 treatment, the maximal inclusion age is not specified in 332 protocols (57.2%), while 159 (27.4%) and 197 (34.0%) do not report whether participants with severe or critical disease forms will be included, respectively. We also could not assess if patients with known risk factors for poorer outcomes would be included in between 74.8% (regarding the inclusion or exclusion of patients with an immunocompromised state) and 93.8% (regarding the inclusion or exclusion of participants with hypertension) of the protocols.

COVID-19 treatment trials interventions

Most trials (349 of 580, 60.2%) study pharmacotherapy (drug medicines), though 92 (15.9%) study traditional Chinese medicine (TCM). The remaining trials (25.0%) evaluate mesenchymal stem cells and natural killer cells, advanced life-support strategies, convalescent plasma and immunoglobulins, and other interventions (table 1).

Considering protocols for which clinical data is available, less than half plan to include participants over the age of 80 (19.7%), patients at critical stage (21.4%), and patients with known risk factors for poorer outcomes (range, 1.6 to 5.5%). When comparing pharmacotherapy, TCM, and trials evaluating other treatment interventions, we found notable differences in the proportion of trials that will include patients with a severe ($P<0.001$) or critical status ($P<0.001$) at baseline, both being smaller among trials evaluating TCM (figure 1).

Considering protocols for which methodological data is available, most trials are non-industry-funded (81.1%), use a randomised design (67.9%), and are conducted in China (47.6%), irrespectively of the intervention under evaluation. Less than half the trials (41.7%) planned to have more than one centre and only 3.0% planned to include centres from countries in

different continents (figure 2). Core clinical outcomes (mortality, clinical status evaluated with WHO scales, and length of hospitalization) are assessed as primary endpoints in only a minority of trials (range, 5.2 to 13.1%). The most commonly reported primary endpoints are respiratory measures (97, 20.8%). The planned median sample size and trial duration are 100 participants (interquartile range, 50 to 260) and 184 days (interquartile range, 94 to 365), respectively. When comparing pharmacotherapy, TCM, and trials evaluating other treatment interventions, we found notable differences in the proportion of trials that will be RCTs (P<0.001), being higher among pharmacotherapy trials, and in the planned median sample sizes (P<0.001), being lowest in trials not evaluating pharmacotherapy or TCM (figure 3).

Pharmacotherapy trials for COVID-19 treatment

The clinical and methodological characteristics of these trials are detailed in the supplementary material.

Of the 349 trials that aim to evaluate drug treatments for COVID-19, most (111, 31.8%) evaluate chloroquine/hydroxychloroquine. Additionally, 89 (25.5%) evaluate antivirals, 65 (18.6%) assess monoclonal antibodies, and 42 (12.0 %) assess a form of interferon, immunomodulators, or immunosuppressants. Notably, the proportion of trials that include patients with severe or critical illness at baseline is different between these groups (P<0.001 for both), both being larger among trials evaluating monoclonal antibodies (89.5% and 45.8%, respectively) and smaller among trials evaluating antivirals (43.9% and 13.2%, respectively). The proportion of trials including patients with COPD, diabetes, cancer, or immunodeficiency is also different across these treatment groups, being larger in chloroquine/hydroxychloroquine trials and smaller in antiviral trials (table and figure in the supplementary material). The planned median trial sample sizes and study durations are also larger in chloroquine/hydroxychloroquine trials and smaller in antiviral trials (table and figure in the supplementary material).

Availability of results and recruitment status in September 2020

We assessed recruitment status and availability of results of the 580 treatment trial protocols registered up to April 19th, 2020, on September 14th, 2020.

66 (11.4%) of trials are reported as “Completed”, 351 (60.5%) as “Recruiting”, 130 (22.4%) as “Not yet recruiting”, 14 (2.4%) as “Suspended”, 11 (1.9%) as “Terminated”, seven (1.2%) as “Withdrawn” and for one (0.2%) recruitment status was unknown.

Of the 18 trials prematurely stopped (classified as “Terminated” or “Withdrawn”) we collected the reasons to stop if explicit in the registries: six were due to low accrual, three were due to availability of new evidence, two for others reason (such as administrative issues among others), and for seven trials reasons to stop were unknown. 14 trials were reported as “Suspended” for the following reasons: six due to low accrual, one due to futility, one due to availability of new evidence, three for other reasons, and three for unknown reasons.

Of the 580 identified treatment trials, 251 (43.3%) have planned to be completed before September 14th, 2020; nevertheless only 33 of these (13.1%) have a recruitment status reported as “Completed” at that time. The majority of these trials are still reported as “Recruiting” (136; 54.2%), 66 (26.3%) are reported as “Not yet recruiting”, six (2.4%) are reported as “Suspended”, seven (2.8%) as “Terminated”, two (0.8%) as “Withdrawn” and one (0.4%) was unknown.

Only 46 trials (7.9%) have any public results available, mainly through journal articles, and only one with results submitted in the registry. Of these 46 trials, 19 are reported as “Completed” in the registry and two as “Terminated”, while 22 are still listed as “Recruiting”, and three as “Not yet recruiting”.

Discussion

On January 30th, 2020, COVID-19 was declared a public health emergency of international concern and on March 11th, it was declared a pandemic. As of our initial search date, April 19th, 1,603,209 cases have been reported worldwide, 54,225 patients were at a serious or critical state, and 169,750 have died.[12] These numbers were increasing by the hour as the world faced a race to mitigate the impact of the disease. Our results suggest that a considerable effort in clinical research has been early

mobilized against COVID-19. The hundreds of trials being conducted worldwide are a motivation for hope. For maximal efficacy of research in infectious disease epidemics, research must be fast, flexible, and integrated with the frontline response.[13]

Adaptive clinical trials,[14, 15] where sample sizes and allocation ratios can be refined, treatments or doses can be abandoned, and focus can move towards patients with a higher likelihood of benefit, may be particularly useful in the current pandemic. A few large trials, notably, the RECOVERY trial and the WHO Solidarity trial, are underway and use an adaptive design. Currently, preliminary results are available confirming the usefulness of this type of trial design in providing informative evidence, namely showing positive results for dexamethasone[16] and lack of benefit for hydroxychloroquine[17] and lopinavir/ritonavir[9]. Another example is the Adaptive COVID-19 Treatment Trial, (ACTT)[18], sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) that lead remdesivir to receive a conditional marketing authorisation by EMA and an initial Emergency Use Authorization (EUA) followed by formal approval of the FDA.

However, with these few exceptions, the research we found seems largely insufficient to reach clear answers for core outcomes in the shortest possible time. Our results suggest that patients at the largest risk of death due to COVID-19 were not being prioritised in clinical trials. This is an important missed opportunity since the high baseline risk means that smaller treatment effects would be more easily detected.[4] Therefore, participants with a higher likelihood of benefit should not only be the focus of clinical research from an ethical point of view, but would be the most efficient population to study in order to identify which treatments are worthwhile pursuing and which are not.

Although most treatment trials use a randomised controlled design, we found that 92 (15.9%) were single-arm trials. These trials are a matter for concern, namely as CFR change considerably over time, and trials using historical controls will likely lead to more false-positive findings.[19] Also of concern is the fact that most treatment trials (58.3%) were not multicentric. It is well documented that evidence from single-centre trials is more prone to bias compared with multicentre trials, and tend to provide larger treatment effects.[20] This is particularly clear in the critical care setting, where many positive single-centre trials have been contradicted by subsequent multicentre trials.[21] Furthermore, few RCTs conducted in intensive care units and using mortality as a primary endpoint show a beneficial impact of the intervention on the survival of patients with critical illness.[22]

Another essential aspect of trial design is the choice of endpoints. While we recognize the importance of surrogate endpoints, which allow faster results to be obtained when compared with core clinical endpoints,[23] the lack of hard and more pragmatic endpoints such as death and length of hospitalisation are causes for concern. To eschew these more clinically relevant endpoints is a methodological mistake that is hard to understand. High-quality information, with as little indirectness as possible, will be key moving forward. For research to permit informed clinical decision-making, this will have to change, and trials must use uniform disease-related definitions. Furthermore, many treatment trials are *a priori* already deemed to fail. The median target sample size of assessed COVID-19 pharmacotherapy trials is 100 participants. This is manifestly insufficient to detect anything but an extremely large treatment effect. For example, regarding trials with mortality as a primary endpoint, only three trials were powered to detect a difference of 50% or more between treatment groups (assuming a baseline risk of 2%). Even assuming a baseline risk of 10%, only 38 trials were adequately powered to detect a difference of 50% or more between treatment groups. In fact, half of the trials evaluating mortality have a sample size of 112 participants or fewer, being only able to identify a treatment effect on mortality over 90% (irrespectively of the baseline risk), which is delusional (supplementary material). On the other hand, the planned trial duration is also relatively short (median of 184 days for overall treatment trials), given the uncertainty regarding the natural history of COVID-19.

Some of our concerns have been increased by the early termination of a clinical trial studying remdesivir, conducted in ten hospitals in Wuhan, China.[24] This trial was to enroll 453 participants, but as the disease in the area was brought under control the number of eligible patients became too small, and recruitment was stopped at 236 participants. This led to a reduced power in the trial, of only 58%, while it was intended to be of 80%. This trial failed to demonstrate any difference in time to clinical improvement with remdesivir (HR 1.23 [95% CI 0.87–1.75]), while, later on, the ACTT trial, an adaptive, larger and adequately powered trial succeeded in showing the usefulness of remdesivir in hospitalized patients (rate ratio for recovery 1.32 [95% CI 1.12-1.55]).[18]

We found that only 18.9% of treatment trials were industry-funded. Although trials done by the initiative of investigators are important, the absence of the efficient and experienced industry trials means that there is considerable room for improvement and effort by part of these multinational corporations. Although we are aware of important efforts by industry to maintain pharmacotherapies available during the crisis, these entities should not forget their essential role in conducting high-quality, high-output clinical research.

In mid-March 2020, the majority of COVID-19 cases worldwide were no longer from continental China, and as of April 19th, 2020, only around 4% of cases were from China.[12] These figures are in clear contrast with the fact that so many treatment trials (47.6%) were conducted exclusively in China. Previous research has suggested that a large proportion of clinical trial data submitted to support new drug registrations in China may be considered to be incomplete or substandard.[25] Therefore, despite the large push in research, we question if the coming flood of data do have enough quality to produce clear answers to critical questions at early stages and the necessary recruitment capability. We are also worried that considerable efforts were wasted in the 92 treatment trials and combined planned target samples of 18,892 participants studying the effect of TCM on COVID-19. We would urge that these resources be put to more promising use.

The main pharmacotherapies under investigation were chloroquine/hydroxychloroquine, antivirals, notably lopinavir/ritonavir, and monoclonal antibodies. We found no substantive methodological differences between trials evaluating these interventions. However, there are differences in patients' clinical characteristics, with monoclonal antibody trials allowing the inclusion of more patients with several and critical illness, as well as participants with relevant comorbidities. Antiviral trials include relatively fewer patients with several and critical illness, and largely exclude participants with COVID-relevant comorbidities.

As of September 14th, 2020, six months after the pandemic declaration, only a minority of these early trials has provided results available to the public. Additionally, according to planned completion dates, 251 trials should have been completed by this date, while only 33 accomplished this commitment. This corresponds to much lower figures than anticipated, considering the trials planned follow-up. Moreover, the information on the recruitment status of the trials often seems to be not updated in the registries, rendering it difficult to interpret the real state of research on this topic. The current available overall results and status from these early 580 treatment trials reinforce our initial worries about the overall inadequacy of these trials to provide clinically relevant conclusions.

Our study has several limitations. First, the data presented focus exclusively on registered trials. Similarly, phase 1 trials may be underrepresented. Second, there is a significant amount of missing or unsubmitted data for certain data fields, which limits the completeness of the analyses and thus the interpretability of the results presented. Third, given the rush to conduct more research, there may be trials underway that had not yet been registered, an important issue given the common nature of retrospective registration.[6] Fourthly, the quality of the available records was largely poor, with inconsistencies and errors throughout. We think that most of the issues have been resolved, though we cannot be certain that nothing was missed.

With the hundreds of trials enrolling thousands of people currently underway, a more efficient and useful approach would be for research bodies such as the WHO, NIH, Inserm, etc. to create a coordinated research response to face the pandemic. The European Medicines Agency has called for similar efforts.[26] We understand that there are political, ethical, administrative, contractual, regulatory, logistic, economic, and societal factors that may hinder research, though these difficulties should be overcome in times of global crisis. Persisting on the path of isolated investigation will likely only lead to futile trials and more death on a global scale. Given the large numbers of people with COVID-19, and given the recent push for more real-world evidence, we consider there to be an urgent need for a global high-quality COVID-19 patient registry, which could be used to detect large beneficial effects[27] and provide relevant evidence for health-care decision making.[28]

Initiatives such as the WHO R&D Blueprint aim to tackle the challenge of generating new evidence during disease outbreaks. We believe that clinical research must be integrated as an essential element of coordinated international response to epidemics. As those are exceptionally difficult contexts for clinical research, tools such as adaptive protocols that could feasibly be integrated into clinical practice, as well as global research networks and platforms, may be of great help to produce

informative research. Due to unpredictable features of new outbreaks, continued enrolment throughout different locations should be advocated, allowing to achieve sufficient participants and combine research efforts.[29]

Conclusions

The current treatment and prophylaxis options are few and built upon very scarce and fragile data. With the proper forward planning, critical questions could have been answered earlier. As clinical investigators, we have the obligation to adjust and improve the research being conducted. The world was not ready to react with the appropriate research to a pandemic. We believe that the scientific community, the pharmaceutical industry, and research agencies could have done better.

Abbreviations

ACTT: Adaptive COVID-19 Treatment Trial; CFR: Case Fatality Rates; ChiCTR: Chinese Clinical Trial Registry; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 2019; EMA: European Medicines Agency; EUA: Emergency Use Authorization; EUCTR: European Clinical Trials Register; FDA: Food and Drug Administration; ICTRP: International Clinical Trials Registry Platform; IQR: interquartile range; NIAID: National Institute of Allergy and Infectious Diseases; RCT: Randomized Controlled Trials; TCM: Traditional Chinese Medicine; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

Joaquim J Ferreira received speaker and consultant fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal and Merck Sharp and Dohme. The remaining authors declare no conflicts of interest.

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Authors' contributions

Research project:

1. Conception, GSD, JC
2. Organization, GSD, JC
3. Execution, BM, GSD, LP, TM

Statistical analysis:

1. Design, JC, NG
2. Execution, NG

3. Review and Critique, BM, GSD, JC, JJF, TM

Manuscript preparation:

1. Writing of the first draft, GSD
2. Review and Critique, BM, JC, JJF, LP, NG, TM

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Availability of data and materials

The datasets supporting the conclusions of this article are available in the following repositories:

1. World Health Organization International Clinical Trials Registry Platform; https://www.who.int/clinical-trials-registry-platform
2. ClinicalTrials.gov; https://clinicaltrials.gov/
3. EU Clinical Trials Register; https://www.clinicaltrialsregister.eu/
4. Chinese Clinical Trial Registry; http://www.chictr.org.cn
5. Cochrane Covid-19 Study Register; https://covid-19.cochrane.org/

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Tables

Table 1. Trials for COVID-19 treatment

	Pharmacotherapy	Traditional Chinese Medicine	Mesenchymal stem cells and NK cells	Advanced life-support strategies	Convalescent plasma and immunoglobulins	Others
Number of trials – no. (%)	349 (60)	92 (16)	39 (7)	27 (5)	35 (6)	44 (8)
Maximal inclusion age – no. (%)						
≥65	115 (33)	56 (61)	26 (67)	10 (37)	12 (34)	17 (39)
≥80	61 (17)	26 (28)	7 (18)	9 (33)	6 (17)	6 (14)
Not specified or unknown*	228 (65)	32 (35)	12 (31)	17 (63)	20 (57)	27 (61)
Inclusion of severe COVID-19 – no. (%)						
Yes	174 (50)	23 (25)	28 (72)	16 (59)	22 (63)	16 (36)
No	86 (25)	30 (33)	2 (5)	10 (37)	4 (11)	14 (32)
No information	89 (26)	39 (42)	9 (23)	1 (4)	9 (26)	14 (32)
Inclusion of critical COVID-19 – no. (%)						
Yes	70 (20)	3 (3)	12 (31)	17 (63)	16 (46)	8 (18)
No	165 (47)	48 (52)	9 (23)	6 (22)	9 (26)	22 (50)
No information	114 (33)	41 (45)	18 (46)	4 (15)	10 (29)	14 (32)
Inclusion of participants with cancer – no. (%)						
Yes	15 (4)	3 (3)	0 (0)	0 (0)	0 (0)	1 (2)
No	49 (14)	31 (34)	27 (69)	3 (11)	4 (11)	11 (25)
No information	285 (82)	58 (63)	12 (31)	24 (89)	31 (89)	32 (73)
Inclusion of participants with COPD – no. (%)						
Yes	16 (5)	3 (3)	0 (0)	1 (4)	0 (0)	0 (0)
No	31 (9)	31 (34)	7 (18)	3 (11)	3 (9)	6 (14)
No information	302 (87)	58 (63)	32 (82)	23 (85)	32 (91)	38 (86)
Inclusion of participants with diabetes – no. (%)						
Yes	16 (5)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)
No	16 (5)	11 (12)	2 (5)	3 (11)	1 (3)	6 (14)
No information	317 (91)	81 (88)	37 (95)	23 (85)	34 (97)	38 (86)
Inclusion of participants with heart disease – no. (%)						

Yes	30 (9)	0 (0)	0 (0)	1 (4)	0 (0)	1 (2)
No	52 (15)	23 (25)	3 (8)	1 (4)	4 (11)	5 (11)
No information	267 (77)	69 (75)	36 (92)	25 (93)	31 (89)	38 (86)
Inclusion of participants with hypertension – no. (%)						
Yes	19 (5)	2 (2)	0 (0)	1 (4)	0 (0)	0 (0)
No	8 (2)	4 (4)	0 (0)	1 (4)	0 (0)	1 (2)
No information	322 (92)	86 (93)	39 (100)	25 (93)	35 (100)	43 (98)
Inclusion of immunocompromised participants – no. (%)						
Yes	9 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No	82 (23)	27 (29)	13 (33)	2 (7)	5 (14)	9 (20)
No information	258 (74)	65 (71)	26 (67)	25 (93)	30 (86)	35 (80)
Main geographical locations – no. (%)	China 110 (32) Single European country 103 (30) United States 47 (13)	China 90 (98) Single African country 1 (1) No information 1 (1)	China 28 (72) Single European country 6 (15) Single American country 2 (5)	China 10 (37) Single European country 9 (33) United States 6 (22)	China 11 (31) Single European country 9 (26) United States 6 (17)	China 21 (48) United States 8 (18) Single European country 7 (16)
Primary endpoints used – no. (%)						
Mortality	43 (13)	7 (8)	3 (8)	8 (30)	9 (26)	5 (11)
Clinical status (WHO Scales)	38 (11)	0 (0)	0 (0)	0 (0)	2 (6)	3 (7)
Length of hospitalization	14 (4)	8 (9)	2 (5)	2 (7)	2 (6)	3 (7)
Randomised trials – no. (%)						
Yes	275 (79)	49 (53)	19 (49)	13 (48)	16 (46)	26 (59)
No	74 (21)	43 (47)	20 (51)	14 (52)	19 (54)	18 (41)
Multicentre trials – no. (%)						
Yes	129 (37)	37 (40)	11 (28)	6 (22)	13 (37)	15 (34)
No	164 (47)	47 (51)	26 (67)	17 (63)	16 (46)	25 (57)
No information	56 (16)	8 (9)	2 (5)	4 (15)	6 (17)	4 (9)
Industry-funded – no. (%)						
Yes	73 (21)	12 (13)	9 (23)	2 (7)	6 (17)	7 (16)

No	276 (79)	80 (87)	30 (77)	25 (93)	29 (83)	37 (84)
Median sample size calculated (IQR) – no.	123.5 (60-333)	120 (72-300)	30 (20-48)	44 (20-190.5)	50 (20-117.5)	70 (40-200)
Median expected trial duration (IQR) – days	181 (98.5-365)	155 (90-337)	314 (188-437.5)	217 (92-396)	214 (92-364)	262.5 (90-381.75)

COPD chronic obstructive pulmonary disease, IQR interquartile range.

Note: The sum of the columns is higher than 580 because some trials assess more than one intervention.

* Most of these trials (93%) specify a minimal inclusion age, without specifying a maximal inclusion age.

Figures

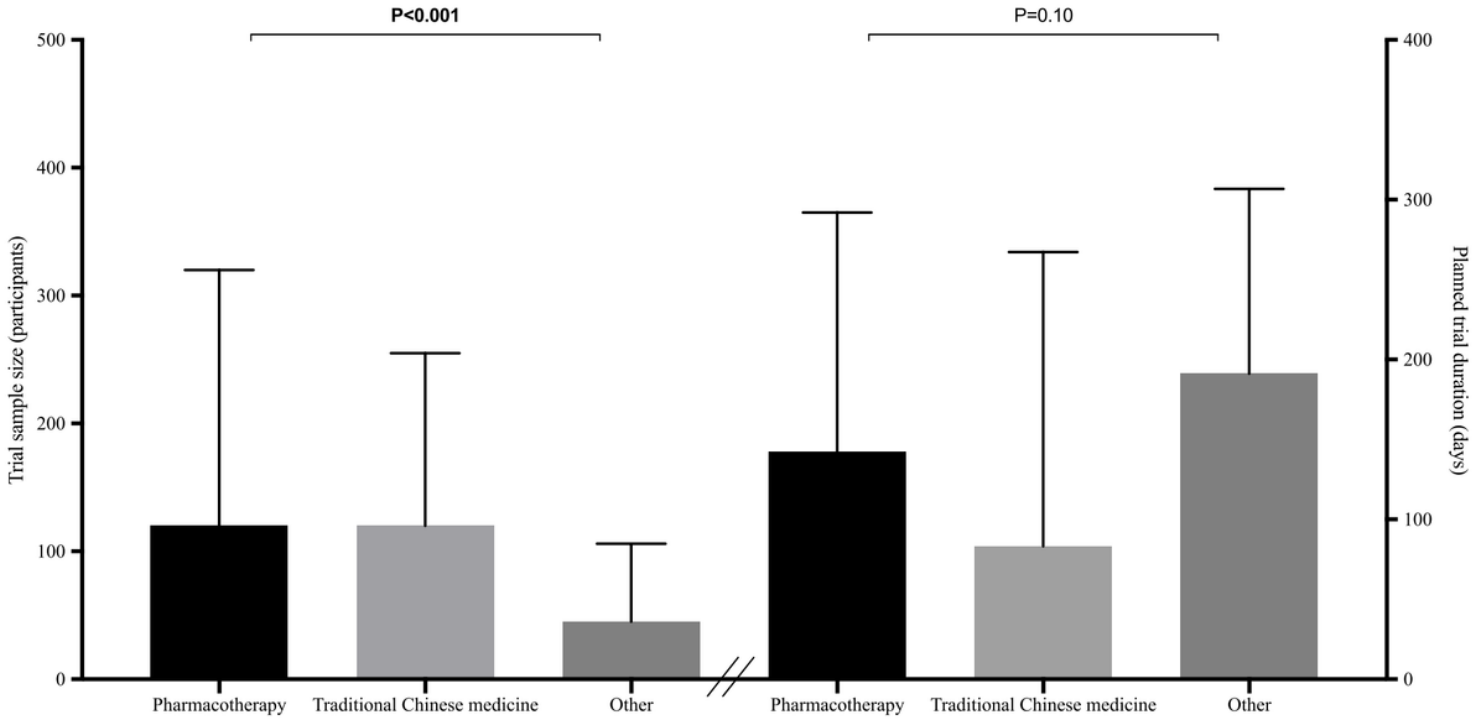

Figure 1

Clinical characteristics of participants included in early COVID-19 treatment trials

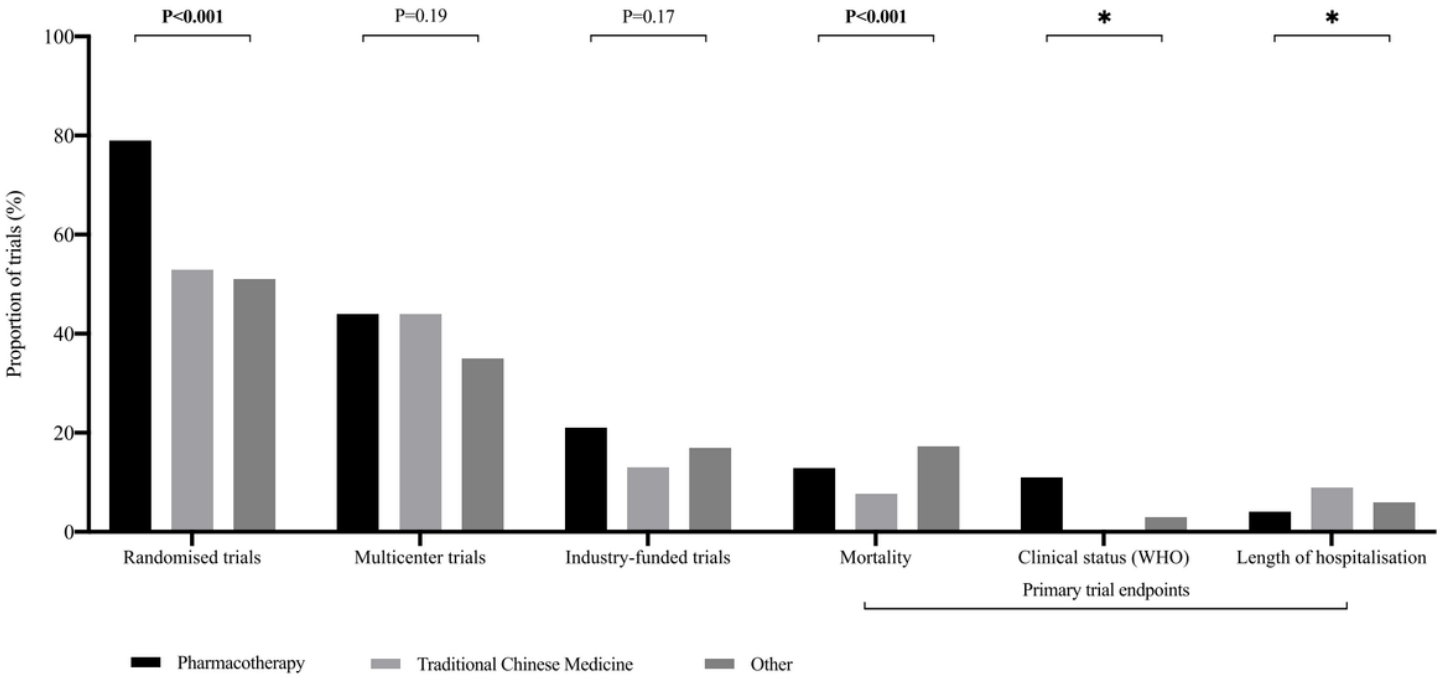

Figure 2

Methodological characteristics of early COVID-19 treatment trials

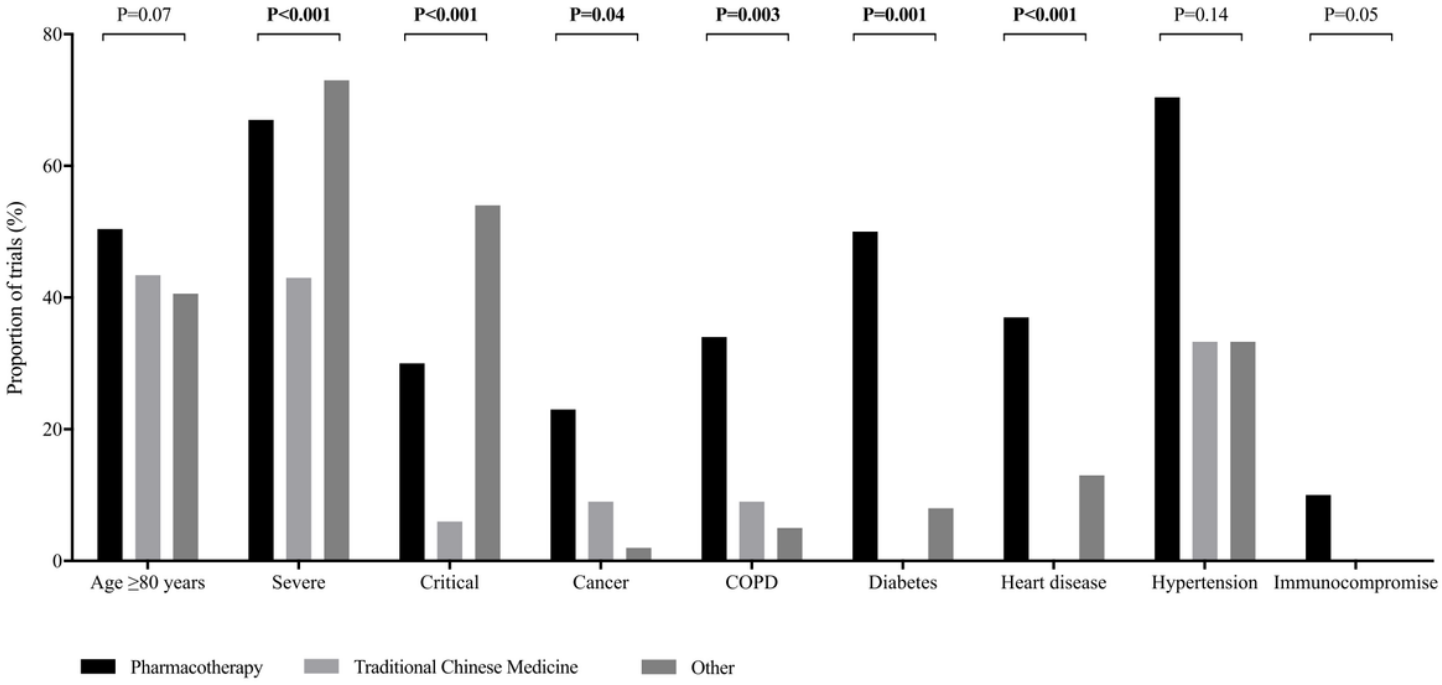

Figure 3

Planned median sample size and trial duration of early COVID-19 treatment trials

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CovidSupplementaryMaterial202012071.docx