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CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19

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ABSTRACT

Objectives. The SARS-CoV-2 (COVID-19) pandemic has prompted many initiatives to identify safe and efficacious treatments, yet little is known regarding where early efforts have focused. We aimed to characterize registered clinical trials assessing drugs or plasma treatments for COVID-19.

Design, setting and participants. Cross-sectional analysis of clinical trials for the treatment of COVID-19 that were registered in the United States or in countries contributing to the World Health Organization's International Clinical Trials Registry Platform (ICTR). Relevant trial entries of drugs or plasma were downloaded on March 26, 2020, de-duplicated, verified with reviews of major medical journals and World Health Organization websites and independently analyzed by two reviewers.

Main outcome(s). Trial intervention, sponsorship, critical design elements and specified outcomes

Results. Overall 201 clinical trials were registered for testing the therapeutic benefits of 92 drugs or plasma, including 64 in monotherapy and 28 different combinations. Only 8 (5.1%) products or combinations involved new molecular entities. The other test therapies had a wide range of prior medical uses, including as antivirals, antimalarials, immunosuppressants and oncology treatments. In 152 trials (75.7%) patients were randomized to treatment or comparator, including 55 trials with some form of blinding and 97 open label studies. The 49 (24.4%) of trials without a randomized design included 29 single armed studies, and 20 trials with some comparison group. Most trial designs featured multiple endpoints. Clinical endpoints were identified in 134 (66.7%) of trials and included COVID-19 symptoms, death, recovery, required intensive care and hospital discharge. Clinical scales were being used in 33 (16.4%) trials, most often measures of oxygenation and critical illness. Surrogate endpoints or biomarkers were studied in 88 (42.3%) of trials, primarily assays of viral load. Although the trials were initiated in more than 17 countries or regions, 100 (49.8%) were registered in China, and 78 (37.8%) in the U.S. Registered trials increased rapidly, with the number of registered trials doubling from March 1 to March 26, 2020.

Conclusions. While accelerating morbidity and mortality from the COVID-19 pandemic has been paralleled by early and rapid clinical investigation, many trials lack features to optimize their scientific value. Global coordination and increased funding of high-quality research may help to maximize scientific progress in rapidly discovering safe and effective treatments.

STRENGTHS AND LIMITATIONS

- We comprehensively assessed the World Health Organization's clinical trials registry network and US clinical trials to identify early clinical trials examining COVID-19 treatments
- In addition to identifying investigational therapies, we also characterized the sponsorship, critical design elements and specified outcomes of each registered clinical trial
- We also report the pharmacological mechanisms and clinical uses for drugs under investigation
- Our analyses was limited to clinical trials of drugs or plasma and many additional trials have been registered since our analysis was performed

INTRODUCTION

Since its identification in China in late 2019, the epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly, with 206 countries and territories reporting cases by April 2020.[1] Although knowledge of the coronavirus disease 2019 (COVID-19) pandemic's true epidemiology has been constrained by the limited availability of testing and surveillance, as of April 1, 2020 nearly one million cases had been confirmed around the world, with over 46,000 deaths and the number of new cases doubling as frequently as every few days.[2]

The impact of the pandemic, as well as uncertainty regarding its future course, has unleashed a wave of biomedical research to identify safe and effective treatments for COVID-19. While new molecular entities are under investigation, many therapies previously approved by regulators for the treatment of other diseases are also being evaluated for repurposing for viral suppression or for lessening the inflammatory consequences of infection.[3] There is also interest in assessing the use of convalescent plasma to treat COVID-19.[4]

Both media[5] and industry[6,7] reports have characterized products being assessed for therapeutic activity against COVID-19. We sought to complement these with a rigorous appraisal of early efforts around the world to identify safe and efficacious treatments to address the pandemic. In addition to identifying investigational therapies, we also characterized the sponsorship, critical design elements and specified outcomes of each registered clinical trial. While our analysis represents an early snapshot of a continually evolving area, it nevertheless provides timely and globally important information for researchers, policy-makers and the general public.

METHODS

Data Sources

We used information from the World Health Organization's (WHO) clinical trials registry network and ClinicalTrials.gov. ClinicalTrials.gov is a registry of public and privately funded clinical trials conducted around the world maintained by the United States (U.S.) National Library of Medicine on behalf of the National Institutes of Medicine. The WHO registry network includes clinical trials from countries including Australia, Brazil, China, South Korea, India, Cuba, European Union, Germany, Iran, Japan, Lebanon, Thailand, Netherlands, Pan Africa, Peru, Sri Lanka and the United Kingdom. Each participating country sends their data to the International Clinical Trials Registry Platform

(ICTRP) maintained by the WHO.[8] Both the WHO registry[9] and ClinicalTrials.gov[10] require that registered trials meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration, and requirements of the International Committee of Medical Journal Editors.

Registry Searches

We downloaded all COVID-19 trials provided by the WHO in a Microsoft Excel spread sheet.[11] The WHO curated all COVID-19 trials published on the ICTRP database in an excel file. Therefore, no search strategy was applied to the ICTRP database. We also performed a manual search of each of the WHO's seventeen network registries, such as EU Clinical trials register to identify additional trials, yielding 21 additional studies. We combined these data with information from the ClincialTrials.gov registry.[12] All searches were last updated on March 26, 2020. To identify trials registered in the U.S., we searched the ClinicalTrials.gov registry for trials related to the 2019 novel coronavirus using keywords "Coronavirus" or "COVID-19" or "COVID19" or "2019 novel coronavirus" or "2019-nCoV" or "SARS-CoV-2" (**eTable 1**). In order to assess whether there were omitted trials, we also searched major medical journals, such as Lancet, New England Journal of Medicine and JAMA, and websites from the World Health Organization, U.S. Centers for Disease Control and Prevention and media aggregators. These searches did not reveal any additional trials to be included in the analysis.

For each product that that was approved by regulators, we searched for information from the European Medicines Agency (EMA)[13] and U.S. Food and Drug Administration (FDA)[14] describing mechanisms of action and approved indications. We searched the pharmaceutical manufacturers' websites and other online sources for information about drugs that were not approved in the European Union or the United States.

Trial Selection

We included all studies conducted on patients diagnosed with COVID-19. First, we selected interventional clinical trials based on the "study type" variable (**eFigure 1**). This variable contains values such as interventional trials, observational studies, expanded access, diagnostic test, basic science, prevention, prognosis, epidemiological research, health services research and screening. Interventional studies are "studies that prospectively assign human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes".[15,16] To be

inclusive of all trials on drugs and plasma, we did not limit our inclusion criteria to randomized trials. Second, we included studies where drugs or plasma was the primary intervention. Since there was not standardized information about the components of each intervention, two individuals (KM, HM) independently reviewed each interventional study to identify any trials of a drug or plasma. Any disagreement was resolved by a third reviewer (GCA). Because study focus was on evaluating drugs or plasma treatments, we excluded trials of stem cell transplants, devices, diagnostic tests, traditional Chinese medicines/herbal medicine, rehabilitation, dietary supplements and psychological interventions. We did not limit any studies based on the outcomes they evaluated. We also excluded one trial with implausible information regarding its study design (a single-arm randomized controlled trial).

Data extraction and management

We extracted the following information from each trial: unique trial number; trial registry source (WHO network registry country or the U.S.), registration date, recruitment status (recruiting, not yet recruiting, withdrawn or cancelled), recruitment country, phase (0, 1, 2, 3, 4, 1-2, 2-3, not applicable, missing), anticipated enrolment, lead sponsor, allocation status (randomized, non-randomized), intervention model (single-arm, parallel, cross-over, factorial, platform trial, sequential), blinding (open, single, double, triple, quadruple,), primary outcome (surrogate/biomarker, clinical scale, clinical outcome) and a website address. Trials that reported recruitment status of completed, active or enrolling by invitation were grouped as recruiting. We used the country address of each facility (i.e., a site that can potentially enroll participants) to identify recruitment countries. Enrolment number reflects the estimated total number of participants to be enrolled or the actual total number of participants enrolled.

We used the primary sponsor and collaborators fields from the U.S. registry, and primary and secondary sponsor fields from the WHO registry to identify the probable lead sponsor. We classified sponsorship as follows: (i) the lead sponsor was considered to be a pharmaceutical company if the primary sponsor was a pharmaceutical company, or a known funding body like the National Institutes of Health (NIH) was neither a primary sponsor or collaborators/secondary sponsor, and at least one collaborator was a pharmaceutical company; (ii) the lead sponsor was a known government research funding agency if identified as such or at least one collaborator was this funder; (iii) the lead sponsor was a hospital if so stated; (iv) all others were classifies as other. For some trials, the study design or

blinding was unclear. In such cases, two reviewers (HM, SE) independently reviewed the registry record in detail and extracted the information. If, after in depth review, study design was still unclear (n=37), we used the following rules to assign intervention model and blinding: (i) trials with a single group were considered as non-randomized and open-label;[17] (ii) trials that reported more than one group were considered having a parallel group design; (iii) trials were considered open-label if blinding was not reported and could not be inferred. We grouped parallel, cross-over, factorial, platform, and sequential intervention trials as multi-arm (>2 trial arms).

Two reviewers (HM, TM) independently reviewed primary outcomes of all trials and assigned them as surrogate or biomarker, clinical scale, or clinical outcomes. Surrogate or biomarker included any measure of SARS-Cov-2 or any blood test; clinical scales included measures of oxygenation, Sequential Organ Failure Assessment (SOFA) score, National Early Warning Score 2 (NEWS2) score, lung injury score or any measure of pulmonary harms; and clinical outcomes included symptoms, clinical improvement scores, intubation, hospitalization or death. Reviewer disagreement was resolved by discussion and consensus.

We identified drugs under investigation for COVID-19 from the experimental and/or control arm of each trial, including multiple drugs when they were studied in combination. Because the trial registries did not record drugs in a standardized format, two pharmacist reviewers (HM, SS) independently extracted this information, converting brand names were scientific names and correcting minor spelling errors. We used the WHO's Anatomical Therapeutic Chemical Classification System to classify drugs in major therapeutic or pharmacological subgroups. For the 18 drugs (e.g., remdesivir) that were not included in the WHO's ATC algorithms, we used product information from the European Medicines Agency, U.S. FDA or the companies' websites to characterize the product.

Analysis

We used descriptive statistics to analyze the extracted data. We summarized the characteristics of all included trials using frequency and percentages. We listed unique drugs under investigation and the number of registered clinical trials for each product. We plotted the number of cumulative trials by their registration date. All data was extracted and stored in an open-access Google Sheet document (Link). The study was considered non-human subject research by the Johns Hopkins University Institutional Review Board. We used SAS version 9.4 (SAS Institute Inc.) for all analyses.

Patient and public involvement

While we did not directly involve patients in the design or conduct of our investigation, our analyses were motivated by a belief that it is important for patients, and the general public, to have accessible, high-quality information regarding the structure and outcomes of clinical trials assessing therapeutics targeting COVID-19.

RESULTS

Characteristics of Clinical Trials

Overall 201 clinical trials were registered for testing the therapeutic benefits of 156 drugs or plasma, including 62 in monotherapy and 92 different combinations (**Table 1**). Although the trials were initiated in more than 17 countries or regions, 100 (49.8%) were registered in China, and 78 (37.8%) in the U.S. Of the 201 trials, 4 (2.0%) were registered in January 2020, 97 (48.2%) in February and 100 (49.8%) between March 1st and March 26, 2020 (**Figure 1**). Nearly 60% of the trials were recruiting patients, and more than half were sponsored by hospitals or universities (55.2%), while about one in five were sponsored by a government (19.4%) and a similar proportion (17.9%) were industry sponsored.

In 152 trials (75.7%) patients were randomized to treatment or comparator, including 55 trials with some form of blinding and 97 open label studies **(Figure 2)**. The 49 (24.4%) of trials without a randomized design included 29 single armed studies, and 20 trials with some comparison group. Of the 201 trials, 54 (26.9%) were parallel group, randomized controlled trials with at least single-blinding.

Primary Endpoints

Most trial designs featured multiple endpoints. Clinical endpoints were identified in 134 (66.7%) of trials and included COVID-19 symptoms, death, recovery, required intensive care and hospital discharge. Clinical scales were being used in 33 (16.4%) trials, most often measures of oxygenation and critical illness assessment instruments. Surrogate endpoints or biomarkers were studied in 88 (42.3%) of trials, primarily assays of viral load. None of the trials assessed patient and public involvement or quality of life as outcome measures.

Study Size

Overall, the studies projected enrolling a median (IQR) of 100 (IQR, 50-240) patients. Notably 54 (26.9%) of trials sought to enroll 50 or fewer patients. At the other extreme, 94 (46.8%) trials sought to enroll 100 or more patients, with 20 (9.6%) studies anticipating enrollment of 500 or more patients.

Therapies Under Evaluation

Overall 92 drugs or plasma were under investigation, including 64 in monotherapy and 28 different combinations (**Table 2**). Only 8 (5.1%) products or combinations involved new molecular entities. The other test therapies had a wide range of prior medical uses; 412 (18.8%) were antivirals, 9 (14.1%) immunosuppressants other than corticosteroids, 4 anticancer drugs (6.3%) 3 (4.7%) antimalarials, 2 (3.1%) corticosteroids, 2 (3.1%) immunostimulants and 2 (3.1%) antithrombotic agents. The 28 different combinations including antivirals, antimalarials, immunosuppressants, immunostimulants and antibacterials (**Table 3**). Of these, nine (32%) were antimalarial/antiviral combinations, seven (25%) antiviral/immunosuppressant combination and six (21%) antiviral/interferon combination.

DISCUSSION

This study characterized the scope, objectives, and content of the current global research program to find effective therapies for COVID-19 as reported to the leading clinical trial registries. These data show that the primary focus of clinical trial research at present is assess whether a wide range of existing therapeutic products might also be effective against acute illnesses caused by the novel SARS-Cov-2 virus. Because one-third of trials exclude clinical endpoints, nearly one half are designed to enroll fewer than 100 patients and two-thirds are open label, many of these studies are likely to yield only preliminary evidence of a given treatment's safety and effectiveness against COVID-19.

Our results indicate that current scientific activity is concentrated in China and the United States, accounting for 87.6% of the studies. Some of the products under investigation, such as remdesivir, have considerable pre-clinical and clinical evidence to support their potential value. In addition to single site trials, several major, multi-site trials of therapies against COVID-19 are also underway. *Solidarity*, announced by the World Health Organization on March 20, 2020, is a multi-center, adaptive, randomized, open-label, five arm trial testing remdesivir, chloroquine/hydroxychloroquine, ritonavir/lopinavir and ritonavir/lopinavir with interferon-beta against standard of care in dozens of countries around the globe.[18] *Discovery*, coordinated by France's National Institute of Health and Medical Research (Inserm), is designed as an add-on trial in Europe and will study the same drugs with

the exclusion of chloroquine.[19] The vast majority of test therapies have been approved for other uses, although 8 new molecular entities are being assessed, a number that is likely to grow as governments and industry invest in new compounds during the coming months.

Our findings provide reason for both optimism and caution. Many registered COVID-19 trials have been designed expediently, and while case series and single-arm trials have value and may provide early signals, randomized study designs provide higher quality evidence and will maximize chances for finding effective and safe treatments during this wave of the pandemic. These trial designs, however, need adequate funding as well as scientific leadership, especially as frontline clinicians are tasked with saving lives. In addition, it is important that surrogate outcomes, biomarkers or clinical scales are strongly and directly linked to what matters most for providers and patients, improved chances of recovery from COVID-19.[20,21]

This study provides early evidence of the benefits of global registries to characterize urgent clinical trial research questions now under investigation. Used wisely by active researchers, these registries can help to identify the most promising avenues for developing new therapies, avoid unnecessary duplication, and define unanswered questions that inevitably arise from early research. The registries also constitute a focal point for developing a more comprehensive program to share protocols and research results. Given the early use of pre-prints prior to peer review and multiple journals publishing results, the global research enterprise needs to enlarge and extend the cooperative effort initiated by these registries.

Limitations

Our analysis was limited to a cross-sectional review of trials registered early in the pandemic with one half the studies registered in the previous month. Many of these studies appeared to be exploratory and not explicitly powered to test a specific drug effect on a pre-specified primary endpoint. In addition, our assessment was limited to drugs and plasma, rather than other treatment modalities under investigation. We did not include trials from Health Canada's Clinical Trials Database because this database does not provide relevant details on trial characteristics. However, if trials are reported in US or WHO database, they are included in our study. We did not apply Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline to evaluate overall quality of clinical trials protocol. Future research can evaluate quality of clinical trials for COVID-19. Finally, our

analysis is only as good as the data that it is based on; the International Clinical Trials Registry Platform (ICTRP) gathers information from more than a dozen contributing countries and despite its value, there remain opportunities to improve the consistency and quality of submitted data from both this platform[22] and ClinicalTrials.gov.[23]

CONCLUSIONS

The global pandemic has galvanized the world's research community, and there are signs of remarkable scientific activity.[24] In this review of clinical trials registered early in course of the pandemic's first wave, we found evidence of rapid clinical investigation of existing antivirals, antimalarials, immunosuppressants and oncology treatments for repurposing against COVID-19. Despite this, many registered trials lack features to optimize their scientific value. Global coordination and increased funding of high-quality research may help to maximize scientific progress in rapidly discovering safe and effective treatments.

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It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

337 **Table 1.** Characteristics of Registered Clinical Trials for SARS-CoV-2 Infection (n=201 trials).

Clinical Trial Characteristics	Total trials (N = 201)
Trial intervention, n (%)	
Drug	188 (93.5)
Plasma	13 (6.5)
Trial registry source, n (%)	
China	100 (49.8)
United States	76 (37.8)
Europe Union	9 (4.5)
Iran	10 (5.0)
Japan	4 (2.0)
ISRCTN	2 (1.0)
Status, n (%)	
Recruiting	120 (59.7)
Not yet recruiting	75 (37.3)
Withdrawn	6 (3.0)
Recruitment country,[a] n (%)	
China	126 (53.9)
Europe	31 (13.3)
Asia (Except China)	18 (7.7)
North America	17 (7.3)
Middle East	13 (5.6)
South America	6 (2.6)
Africa	1 (0.4)
Not reported	22 (9.4)
Phase, n (%)	
0	37 (18.4)
1 or 1/2	5 (2.5)
2	32 (15.9)
2/3	16 (8.0)
3	33 (16.4)
4	51 (24.9)
Not applicable	26 (12.9)
Missing	2 (1.0)
Lead sponsor, n (%)	
Hospitals	111 (55.2)
Industry	36 (17.9)
Government	39 (19.4)
Other[b]	7 (3.5)
Not reported	8 (4.0)

[a]Percentages may exceed 100% as categories not mutually exclusive
[b]Includes foundations and disease trial networks
ISRCTN International Standard Randomised Controlled Trial Number
Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

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Table 1 (con't)

Anticipated enrolment, n (%)	
Median (IQR)	100 (50-240)
≤50	54 (26.9)
51-100	53 (26.4)
≥100	94 (46.8)
Outcome,[a] n (%)	
Surrogate/biomarker	85 (42.3)
Clinical scale	33 (16.4)
Clinical outcome	134 (66.7)

Table 2. Products Being Assessed in Registered Clinical Trials for SARS-COV-2 Infection.

Major drug class and drugs	Registered trials, N[a]	Pharmacologic mechanism	Clinical Uses
Antimalarials	**50**		
Chloroquine or hydroxychloroquine	49	Inhibit certain enzymes by interacting with DNA; possible antiviral effect on SARS-CoV through changing the glycosylation of ACE2 receptor and spike protein	Malaria, extraintestinal amebiasis, lupus erythematosus, rheumatoid Arthritis
Dihydroartemisinin/piperaquine	1	Blocks a step in P. falciparum parasite's metabolism needed for its survival	Malaria
Antivirals[b]	**67**		
Asc09/ritonavir	2	HIV-1 protease inhibitor	Investigational drug for HIV (China)
Azvudine	4	Reverse transcriptase inhibitor	Investigational drug for HIV-1
Baloxavir	2	Polymerase acidic (PA) endonuclease inhibitor	Influenza
Danoprevir/ritonavir	4	Danoprevir inhibits hepatitis virus C NS3/4A protease inhibitor;	Investigational drug for Hepatitis C
Darunavir/cobicistat	1	Darunavir inhibits HIV-1 protease enzyme, thus slowing down multiplication of HIV	HIV-1
Favipiravir	11	Inhibits RNA polymerase and prevents replication of the viral genome	Influenza (Japan)
Lopinavir/ritonavir	16	Lopinavir inhibits HIV-1 protease enzyme, thus slowing down multiplication of HIV	HIV-1
Remdesivir	10	Nucleoside analogue; inhibit the action of RNA polymerase; tested for Ebola, MERS, SARS	None; Investigational medicine
Ribavirin	1	Inhibition of viral RNA and protein synthesis	Hepatitis C
Oseltamivir	2	Inhibitor of influenza virus neuraminidase affecting release of viral particles	Influenza
Umifenovir	6	Inhibits membrane fusion in influenza virus	Influenza (Russia and China)
Sofosbuvir/ledipasvir	1	Sofosbuvir inhibits HCV NS5B RNA; ledipasvir inhibits HCV NS5A inhibitor	Hepatitis C
Different antiviral combinations[c]	**7**		
Immunosuppressants	**27**		
Adalimumab	1	Blocks tumor necrosis factor – α, thereby reducing inflammation and other symptoms of the disease	Rheumatoid arthritis, psoriatic arthritis, Juvenile idiopathic arthritis, Crohn's disease, axial spondyloarthritis, Plaque psoriasis
Baricitinib	2	Janus kinase inhibitor	Rheumatoid arthritis
Fingolimod	1	Sphingosine 1-phosphate receptor modulator	Multiple sclerosis
Ixekizumab	1	Interleukin-17A antagonist	Plaque psoriasis, psoriatic arthritis

Leflunomide	1	Pyrimidine synthesis inhibitor	Rheumatoid arthritis, psoriatic arthritis
Pirfenidone	3	Not yet known; reduce fibroblasts production	Idiopathic pulmonary fibrosis
Sarilumab	4	Interleukin-6 receptor antagonist	Rheumatoid arthritis
Thalidomide	2	Not fully known; it has immunomodulatory, antiinflammatory and antiangiogenic properties	Multiple myeloma, erythema nodosum leprosum
Tocilizumab	11	Interleukin-6 receptor antagonist	Rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, cytokine release syndrome
Immunostimulants	**16**		
Interferon	15	Recombinant cytokine with antiviral properties	Hepatitis B, hepatitis C, leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, malignant melanoma
Sargramostim	1	Human granulocyte-macrophage colony-stimulating factor	Acute myeloid leukemia, transplantation
Anticancer drugs	**7**		
Bevacizumab	2	Vascular endothelial growth factor-specific angiogenesis inhibitor	Several types of cancer; for example, colon, lung, breast
Colchicine	2	Tubulin disruption	Gout flare, familial Mediterranean fever
Programmed death receptor-1 (PD-1) antagonists	2	Binds to PD-1 found on T cells, thereby inhibiting T cell proliferation	Several types of cancer; for example, melanoma, lung, kidney
Ruxolitinib	1	Janus kinases inhibitor	Myelofibrosis, polycythaemia vera
Plasma	**14**		
Dexamethasone	1	Apoptosis of multiple myeloma cells	Multiple myeloma
Methylprednisolone	5	Binds to nuclear receptors to dampen proinflammatory cytokines	Several uses; for example, endocrine, rheumatic and collagen disorders
Immunoglobulins	**3**		Several autoimmune, infectious, and idiopathic diseases
Antithrombotic agents	**3**		
Heparin	2	Inactivation of Factor Xa and Factor IIa	Deep vein thrombosis, pulmonary embolism
Enoxaparin	1		
Antifibrinolytics (Proteinase inhibitors)	**2**		
Camostat	1	Serine protease inhibitor	Chronic pancreatitis, postoperative reflux esophagitis (Japan)
Ulinastat	1	Urinary trypsin inhibitor	Acute pancreatitis, shock (Japan)
Expectorants (Mucolytics)	**2**		
Acetylcysteine	1	Mucolytic agent	Abnormal, viscid, or inspissated mucous secretions
Bromhexine	1	Mucolytic agent	Congestion and cough

Other drugs	**35**		
Aviptadil	1	Analogue of vasoactive intestinal polypeptide	Acute lung injury, sarcoidosis (Europe)
Azithromycin	1	Inhibits bacterial protein synthesis	Mild to moderate infections
Carrimycin	2	Inhibit protein synthesis by binding to ribosomes of the bacteria	Tuberculosis
Camrelizumab	1	Monoclonal antibody; PD-1 inhibitor	Refractory classical Hodgkin lymphoma (China)
CD24Fc	1	Recombinant fusion protein that targets a novel immune pathway checkpoint	Investigational drug
Dexmedetomidine	1	Selective alpha2-adrenergic agonist	Sedation
Escin	2	Inhibition of an inflammatory response at cellular level	Decongestant, reduction of swelling following injuries
GD31 (Nucleoside analog)	1	Nucleoside analogues	Not found
Jakotinib	1	Janus kinase inhibitor	Investigational drug (China)
Losartan	2	Angiotensin II receptor blockers	Hypertension
Meformin	1	Decreases hepatic production and intestinal absorption of glucose, improves insulin sensitivity	Diabetes Mellitus
Meplazumab	1	Humanized anti-CD147 antibody	Investigational drug
Nitric oxide	5	Vasodilating agent	Hypoxic respiratory failure in neonates
Noscapine	1	Opium alkaloid	Cough suppressant
PUL-042	2	Agonists of Toll-like receptors	Investigational drug
Polyinosinic-polycytidylic acid	1	Upregulation of antitumor genes and the induction of cell apoptosis	**Possible anticancer activity**
Recombinant human angiotensin-converting enzyme 2	1	Renin-angiotensin system peptidase	Possible heart failure therapy
Recombinant human interleukin-2	1	T cell growth factor	Melanoma and renal cell carcinoma
Recombinant human granulocyte colony stimulating factor (rhG-CSF)	1	Mediating T cell tolerance	Neutrophil-mediated inflammatory disease
Sildenafil (Urologicals)	1	Sigma receptor agonist activity	Erectile dysfunction
Suramin (Antiprotozoals)	1	Macrofilaricidal	African sleeping sickness and river blindness (Africa)
Thymosin	3	5-Da polypeptide hormone	Investigational drug for cancer
Tranilast	1	Hematopoietic prostaglandin D synthase inhibitor	bronchial asthma, keloid, hypertrophic scar, and allergic disorders (Japan and South Korea)
Triazavirin	1	Guanine nucleotide analogue that inhibits RNA synthesis	Influenza A and B infections (Russia)
Antiviral + Immunosuppressants[d]	**2**		

Antimalarials + Antibacterial[e]	**2**
Antimalarials + Antivirals[f]	**10**
Antivirals + Interferon[g]	**13**
Other combinations[h]	**3**

[a] Column total exceeds 202 as some trials examine multiple drugs; [b] Ritonavir, cobicistat inhibits CYP3A metabolism and increases blood concentration of the other antiviral drug; [c,d,e,f,g,h] Details on drug combinations are provided in eTable 2; [i] One trial did not specify type of corticosteroid

Table 3. Drug Combinations Under Investigation for SARS-COV-2 Infection (n=28 combinations).

	Registered trials, N
Different antiviral combinations	7
Asc09f (Asc09/ritonavir) + oseltamivir	1
Darunavir/ritonavir + oseltamivir	1
Favipiravir + lopinavir/ritonavir	1
Lopinavir/ritonavir + oseltamivir	1
Lopinavir/ritonavir + emtritabine/tenofovir	1
Ritonavir + oseltamivir	1
Sofosbuvir + daclatasvir	1
Immunosuppressants combination	
Tocilizumab + adamumab	1
Antiviral + Immunosuppressants	2
Favipiravir + tocilizumab	2
Antimalarials + Antibacterial	2
Hydroxychloroquine + azithromycin	2
Antimalarials + Antivirals	10
Darunavir/cobicistat + hydroxychloroquine	1
Darunavir/ritonavir + favipiravir + chloroquine	1
Darunavir/ritonavir + oseltamivir + chloroquine	1
Favipiravir + chloroquine	2
Hydroxychloroquine + lopinavir or atazanavir/ritonavir	1
Hydroxychloroquine + oseltamivir + lopinavir + interferon	1
Lopinavir/ritonavir + chloroquine	1
Lopinavir/ritonavir + hydroxychloroquine	1
Oseltamivir + chloroquine	1
Antivirals + Interferon	13
Asc09/ritonavir + interferon	1
Favipiravir + interferon	1
Lopinavir/ritonavir + interferon	6
Ribavirin + interferon	2
Ribavirin + lopinavir/ritonavir + interferon	1
Umifenovir + interferon	2
Other combinations	3
Darunavir/cobicistat + thymosin	1
Lopinavir/ritonavir + thymosin	1
Ebastine + interferon + lopinavir	1

Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

eTable 1. Search Strategy.

Search strategy	"COVID-19" OR "COVID 19" OR "COVID19" OR "COVID2019" OR "COVID 2019" OR "COVID-2019" OR "novel coronavirus" OR "new coronavirus" OR "novel corona virus" OR "new corona virus" OR "SARS-CoV-2" OR "SARSCoV2" OR "SARS-CoV2" OR "2019nCoV" OR "2019-nCoV" OR "2019 coronavirus" OR "2019 corona virus" OR "coronavirus disease 2019" OR "severe acute respiratory syndrome coronavirus 2" OR "sars-coronavirus-2" OR "coronavirus disease 2019" OR "corona virus disease 2019"

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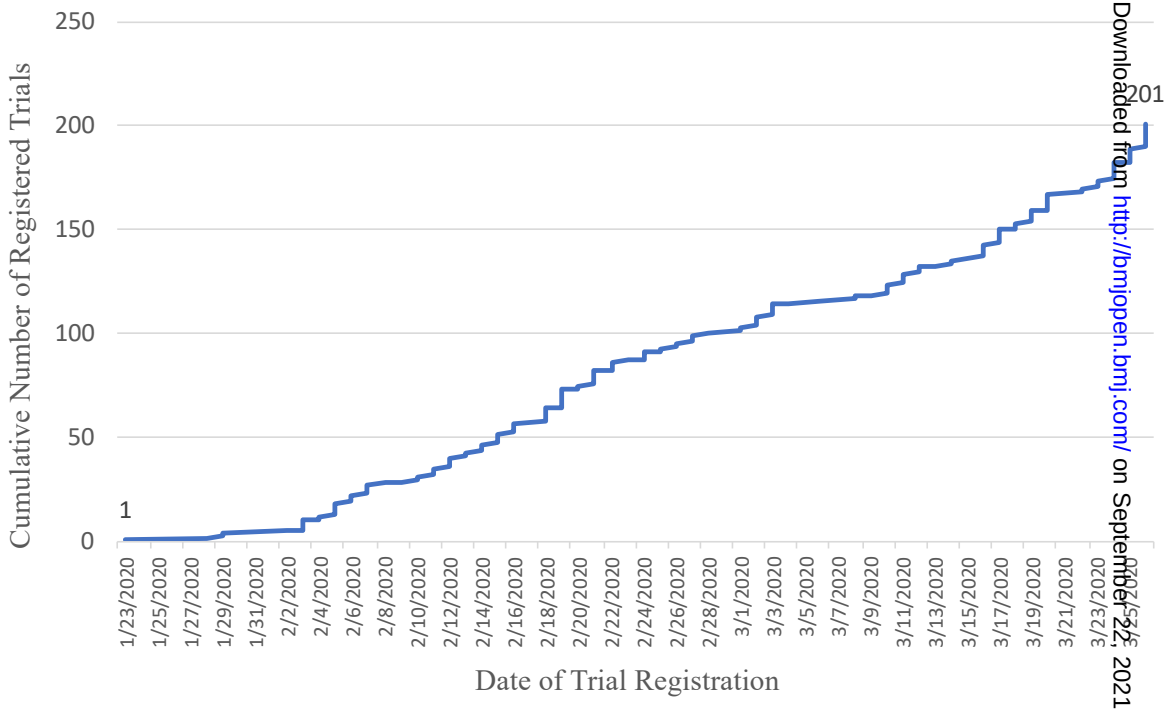
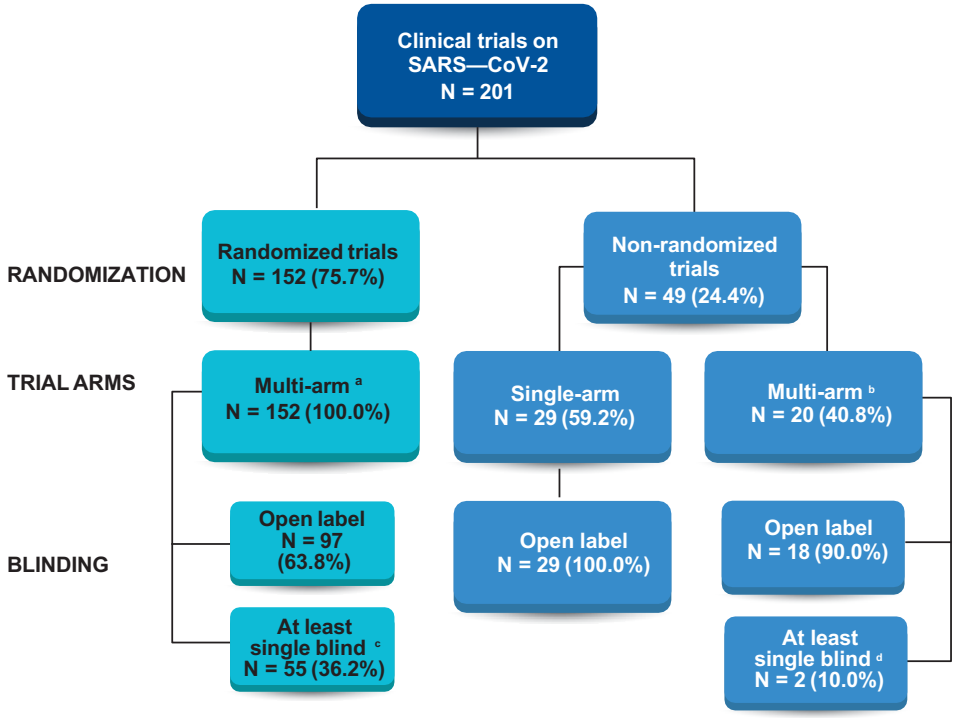
(Accessed April 1, 2020).

Figure 1. Cumulative Number of Registered Clinical Trials of Products for SARS-CoV-2 Infection.



Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

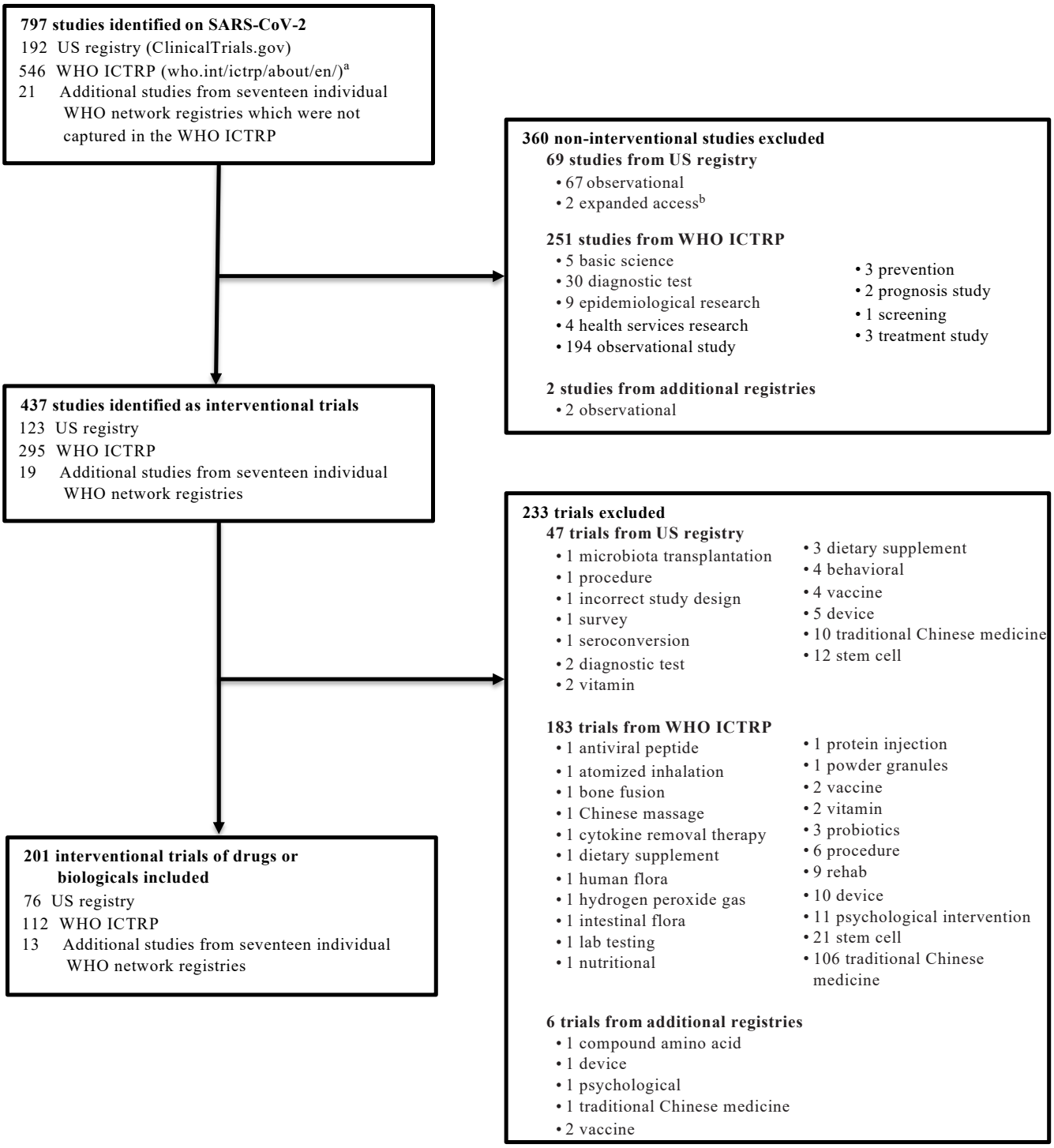
Figure 2. Study Designs of Registered Clinical Trials of Products for SARS-CoV-2 Infection (N=201 trials).



[a] Includes 147 parallel, 1 platform and 4 sequential trials; [b] Includes 1 crossover, 1 factorial, 17 parallel and 1 historical control arm trials; [c] Includes 14 single, 5 at least single, 16 double, 2 triple and 18 quadruple blinded trials; [d] Includes 2 double blind trials

Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

eFigure 1. Study Selection Flowchart



ICTRP International Clinical Trials Registry Platform; **WHO** World Health Organization

[a] To avoid double counting we excluded 121 studies which were originally registered in the US registry

[b] Expanded access refers to study designs where investigational drugs are provided to patients who cannot participate in clinical trial

Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, eFigure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, 8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9, 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19

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CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19

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None

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Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. HBM, SE, TJM and JS have no disclosures to report.

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ABSTRACT

Objectives. The SARS-CoV-2 (COVID-19) pandemic has prompted many initiatives to identify safe and efficacious treatments, yet little is known regarding where early efforts have focused. We aimed to characterize registered clinical trials assessing drugs or plasma treatments for COVID-19.

Design, setting and participants. Cross-sectional analysis of clinical trials for the treatment of COVID-19 that were registered in the United States or in countries contributing to the World Health Organization's International Clinical Trials Registry Platform (ICTR). Relevant trial entries of drugs or plasma were downloaded on March 26, 2020, de-duplicated, verified with reviews of major medical journals and World Health Organization websites and independently analyzed by two reviewers.

Main outcome(s). Trial intervention, sponsorship, critical design elements and specified outcomes

Results. Overall 201 clinical trials were registered for testing the therapeutic benefits of 92 drugs or plasma, including 64 in monotherapy and 28 different combinations. Only 8 (5.1%) products or combinations involved new molecular entities. The other test therapies had a wide range of prior medical uses, including as antivirals, antimalarials, immunosuppressants and oncology treatments. In 152 trials (75.7%) patients were randomized to treatment or comparator, including 55 trials with some form of blinding and 97 open label studies. The 49 (24.4%) of trials without a randomized design included 29 single armed studies, and 20 trials with some comparison group. Most trial designs featured multiple endpoints. Clinical endpoints were identified in 134 (66.7%) of trials and included COVID-19 symptoms, death, recovery, required intensive care and hospital discharge. Clinical scales were being used in 33 (16.4%) trials, most often measures of oxygenation and critical illness. Surrogate endpoints or biomarkers were studied in 88 (42.3%) of trials, primarily assays of viral load. Although the trials were initiated in more than 17 countries or regions, 100 (49.8%) were registered in China, and 78 (37.8%) in the U.S. Registered trials increased rapidly, with the number of registered trials doubling from March 1 to March 26, 2020.

Conclusions. While accelerating morbidity and mortality from the COVID-19 pandemic has been paralleled by early and rapid clinical investigation, many trials lack features to optimize their scientific value. Global coordination and increased funding of high-quality research may help to maximize scientific progress in rapidly discovering safe and effective treatments.

STRENGTHS AND LIMITATIONS

- We comprehensively assessed the World Health Organization's clinical trials registry network and US clinical trials to identify early clinical trials examining COVID-19 treatments
- In addition to identifying investigational therapies, we also characterized the sponsorship, critical design elements and specified outcomes of each registered clinical trial
- We also report the pharmacological mechanisms and clinical uses for drugs under investigation
- Our analyses was limited to clinical trials of drugs or plasma and many additional trials have been registered since our analysis was performed

INTRODUCTION

Since its identification in China in late 2019, the epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly, with 206 countries and territories reporting cases by April 2020.[1] Although knowledge of the coronavirus disease 2019 (COVID-19) pandemic's true epidemiology has been constrained by the limited availability of testing and surveillance, as of April 1, 2020 nearly one million cases had been confirmed around the world, with over 46,000 deaths and the number of new cases doubling as frequently as every few days.[2]

The impact of the pandemic, as well as uncertainty regarding its future course, has unleashed a wave of biomedical research to identify safe and effective treatments for COVID-19. While new molecular entities are under investigation, many therapies previously approved by regulators for the treatment of other diseases are also being evaluated for repurposing for viral suppression or for lessening the inflammatory consequences of infection.[3] There is also interest in assessing the use of convalescent plasma to treat COVID-19.[4]

Both media[5] and industry[6,7] reports have characterized products being assessed for therapeutic activity against COVID-19. We sought to complement these with a rigorous appraisal of early efforts around the world to identify safe and efficacious treatments to address the pandemic. In addition to identifying investigational therapies, we also characterized the sponsorship, critical design elements and specified outcomes of each registered clinical trial. While our analysis represents an early snapshot of a continually evolving area, it nevertheless provides timely and globally important information for researchers, policy-makers and the general public.

METHODS

Data Sources

We used information from the World Health Organization's (WHO) clinical trials registry network and ClinicalTrials.gov. ClinicalTrials.gov is a registry of public and privately funded clinical trials conducted around the world maintained by the United States (U.S.) National Library of Medicine on behalf of the National Institutes of Medicine. The WHO registry network includes clinical trials from countries including Australia, Brazil, China, South Korea, India, Cuba, European Union, Germany, Iran, Japan, Lebanon, Thailand, Netherlands, Pan Africa, Peru, Sri Lanka and the United Kingdom.

Each participating country sends their data to the International Clinical Trials Registry Platform (ICTRP) maintained by the WHO.[8] Both the WHO registry[9] and ClinicalTrials.gov[10] require that registered trials meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration, and requirements of the International Committee of Medical Journal Editors.

Registry Searches

We downloaded all COVID-19 trials provided by the WHO in a Microsoft Excel spread sheet.[11] The WHO curated all COVID-19 trials published on the ICTRP database in an excel file. Therefore, no search strategy was applied to the ICTRP database. We also performed a manual search of each of the WHO's seventeen network registries, such as EU Clinical trials register to identify additional trials, yielding 21 additional studies. We combined these data with information from the ClincialTrials.gov registry.[12] All searches were last updated on March 26, 2020. To identify trials registered in the U.S., we searched the ClinicalTrials.gov registry for trials related to the 2019 novel coronavirus using keywords "Coronavirus" or "COVID-19" or "COVID19" or "2019 novel coronavirus" or "2019-nCoV" or "SARS-CoV-2" (**eTable 1)**. In order to assess whether there were omitted trials, we also searched major medical journals, such as Lancet, New England Journal of Medicine and JAMA, and websites from the World Health Organization, U.S. Centers for Disease Control and Prevention and media aggregators. These searches did not reveal any additional trials to be included in the analysis.

For each product that that was approved by regulators, we searched for information from the European Medicines Agency (EMA)[13] and U.S. Food and Drug Administration (FDA)[14] describing mechanisms of action and approved indications. We searched the pharmaceutical manufacturers' websites and other online sources for information about drugs that were not approved in the European Union or the United States.

Trial Selection

We included all studies conducted on patients diagnosed with COVID-19. First, we selected interventional clinical trials based on the "study type" variable (**eFigure 1)**. This variable contains values such as interventional trials, observational studies, expanded access, diagnostic test, basic science, prevention, prognosis, epidemiological research, health services research and screening. Interventional studies are "studies that prospectively assign human participants or groups of humans to

one or more health-related interventions to evaluate the effects on health outcomes".[15,16] To be inclusive of all trials on drugs and plasma, we did not limit our inclusion criteria to randomized trials. Second, we included studies where drugs or plasma was the primary intervention. Since there was not standardized information about the components of each intervention, two individuals (KM, HM) independently reviewed each interventional study to identify any trials of a drug or plasma. Any disagreement was resolved by a third reviewer (GCA). Because study focus was on evaluating drugs or plasma treatments, we excluded trials of stem cell transplants, devices, diagnostic tests, traditional Chinese medicines/herbal medicine, rehabilitation, dietary supplements and psychological interventions. We did not limit any studies based on the outcomes they evaluated. We also excluded one trial with implausible information regarding its study design (a single-arm randomized controlled trial).

Data extraction and management

We extracted the following information from each trial: unique trial number; trial registry source (WHO network registry country or the U.S.), registration date, recruitment status (recruiting, not yet recruiting, withdrawn or cancelled), recruitment country, phase (0, 1, 2, 3, 4, 1-2, 2-3, not applicable, missing), anticipated enrolment, lead sponsor, allocation status (randomized, non-randomized), intervention model (single-arm, parallel, cross-over, factorial, platform trial, sequential), blinding (open, single, double, triple, quadruple,), primary outcome (surrogate/biomarker, clinical scale, clinical outcome) and a website address. Trials that reported recruitment status of completed, active or enrolling by invitation were grouped as recruiting. We used the country address of each facility (i.e., a site that can potentially enroll participants) to identify recruitment countries. Enrolment number reflects the estimated total number of participants to be enrolled or the actual total number of participants enrolled.

We used the primary sponsor and collaborators fields from the U.S. registry, and primary and secondary sponsor fields from the WHO registry to identify the probable lead sponsor. We classified sponsorship as follows: (i) the lead sponsor was considered to be a pharmaceutical company if the primary sponsor was a pharmaceutical company, or a known funding body like the National Institutes of Health (NIH) was neither a primary sponsor or collaborators/secondary sponsor, and at least one collaborator was a pharmaceutical company; (ii) the lead sponsor was a known government research funding agency if identified as such or at least one collaborator was this funder; (iii) the lead sponsor

was a hospital if so stated; (iv) all others were classifies as other. For some trials, the study design or blinding was unclear. In such cases, two reviewers (HM, SE) independently reviewed the registry record in detail and extracted the information. If, after in depth review, study design was still unclear (n=37), we used the following rules to assign intervention model and blinding: (i) trials with a single group were considered as non-randomized and open-label;[17] (ii) trials that reported more than one group were considered having a parallel group design; (iii) trials were considered open-label if blinding was not reported and could not be inferred. We grouped parallel, cross-over, factorial, platform, and sequential intervention trials as multi-arm (>2 trial arms).

Two reviewers (HM, TM) independently reviewed primary outcomes of all trials and assigned them as surrogate or biomarker, clinical scale, or clinical outcomes. Surrogate or biomarker included any measure of SARS-Cov-2 or any blood test; clinical scales included measures of oxygenation, Sequential Organ Failure Assessment (SOFA) score, National Early Warning Score 2 (NEWS2) score, lung injury score or any measure of pulmonary harms; and clinical outcomes included symptoms, clinical improvement scores, intubation, hospitalization or death. Reviewer disagreement was resolved by discussion and consensus.

We identified drugs under investigation for COVID-19 from the experimental and/or control arm of each trial, including multiple drugs when they were studied in combination. Because the trial registries did not record drugs in a standardized format, two pharmacist reviewers (HM, SS) independently extracted this information, converting brand names were scientific names and correcting minor spelling errors. We used the WHO's Anatomical Therapeutic Chemical Classification System to classify drugs in major therapeutic or pharmacological subgroups. For the 18 drugs (e.g., remdesivir) that were not included in the WHO's ATC algorithms, we used product information from the European Medicines Agency, U.S. FDA or the companies' websites to characterize the product.

Analysis

We used descriptive statistics to analyze the extracted data. We summarized the characteristics of all included trials using frequency and percentages. We listed unique drugs under investigation and the number of registered clinical trials for each product. We plotted the number of cumulative trials by their registration date. All data was extracted and stored in an open-access Google Sheet document

(Link). The study was considered non-human subject research by the Johns Hopkins University Institutional Review Board. We used SAS version 9.4 (SAS Institute Inc.) for all analyses.

Patient and public involvement

While we did not directly involve patients in the design or conduct of our investigation, our analyses were motivated by a belief that it is important for patients, and the general public, to have accessible, high-quality information regarding the structure and outcomes of clinical trials assessing therapeutics targeting COVID-19.

RESULTS

Characteristics of Clinical Trials

Overall 201 clinical trials were registered for testing the therapeutic benefits of 156 drugs or plasma, including 62 in monotherapy and 92 different combinations (**Table 1**). Although the trials were initiated in more than 17 countries or regions, 100 (49.8%) were registered in China, and 78 (37.8%) in the U.S. Of the 201 trials, 4 (2.0%) were registered in January 2020, 97 (48.2%) in February and 100 (49.8%) between March 1st and March 26, 2020 (**Figure 1**). Nearly 60% of the trials were recruiting patients, and more than half were sponsored by hospitals or universities (55.2%), while about one in five were sponsored by a government (19.4%) and a similar proportion (17.9%) were industry sponsored.

In 152 trials (75.7%) patients were randomized to treatment or comparator, including 55 trials with some form of blinding and 97 open label studies **(Figure 2)**. The 49 (24.4%) of trials without a randomized design included 29 single armed studies, and 20 trials with some comparison group. Of the 201 trials, 54 (26.9%) were parallel group, randomized controlled trials with at least single-blinding.

Primary Endpoints

Most trial designs featured multiple endpoints. Clinical endpoints were identified in 134 (66.7%) of trials and included COVID-19 symptoms, death, recovery, required intensive care and hospital discharge. Clinical scales were being used in 33 (16.4%) trials, most often measures of oxygenation and critical illness assessment instruments. Surrogate endpoints or biomarkers were studied in 88

(42.3%) of trials, primarily assays of viral load. None of the trials assessed patient and public involvement or quality of life as outcome measures.

Study Size

Overall, the studies projected enrolling a median (IQR) of 100 (IQR, 50-240) patients. Notably 54 (26.9%) of trials sought to enroll 50 or fewer patients. At the other extreme, 94 (46.8%) trials sought to enroll 100 or more patients, with 20 (9.6%) studies anticipating enrollment of 500 or more patients.

Therapies Under Evaluation

Overall 92 drugs or plasma were under investigation, including 64 in monotherapy and 28 different combinations (**Table 2**). Only 8 (5.1%) products or combinations involved new molecular entities. The other test therapies had a wide range of prior medical uses; 412 (18.8%) were antivirals, 9 (14.1%) immunosuppressants other than corticosteroids, 4 anticancer drugs (6.3%) 3 (4.7%) antimalarials, 2 (3.1%) corticosteroids, 2 (3.1%) immunostimulants and 2 (3.1%) antithrombotic agents. The 28 different combinations including antivirals, antimalarials, immunosuppressants, immunostimulants and antibacterials (**Table 3**). Of these, nine (32%) were antimalarial/antiviral combinations, seven (25%) antiviral/immunosuppressant combination and six (21%) antiviral/interferon combination.

DISCUSSION

This study characterized the scope, objectives, and content of the current global research program to find effective therapies for COVID-19 as reported to the leading clinical trial registries. These data show that the primary focus of clinical trial research at present is assess whether a wide range of existing therapeutic products might also be effective against acute illnesses caused by the novel SARS-Cov-2 virus. Because one-third of trials exclude clinical endpoints, nearly one half are designed to enroll fewer than 100 patients and two-thirds are open label, many of these studies are likely to yield only preliminary evidence of a given treatment's safety and effectiveness against COVID-19.

Our results indicate that current scientific activity is concentrated in China and the United States, accounting for 87.6% of the studies. Some of the products under investigation, such as remdesivir, have considerable pre-clinical and clinical evidence to support their potential value. In addition to single site trials, several major, multi-site trials of therapies against COVID-19 are also underway. *Solidarity*,

announced by the World Health Organization on March 20, 2020, is a multi-center, adaptive, randomized, open-label, five arm trial testing remdesivir, chloroquine/hydroxychloroquine, ritonavir/lopinavir and ritonavir/lopinavir with interferon-beta against standard of care in dozens of countries around the globe.[18] *Discovery*, coordinated by France's National Institute of Health and Medical Research (Inserm), is designed as an add-on trial in Europe and will study the same drugs with the exclusion of chloroquine.[19] The vast majority of test therapies have been approved for other uses, although 8 new molecular entities are being assessed, a number that is likely to grow as governments and industry invest in new compounds during the coming months.

Our findings provide reason for both optimism and caution. Many registered COVID-19 trials have been designed expediently, and while case series and single-arm trials have value and may provide early signals, randomized study designs provide higher quality evidence and will maximize chances for finding effective and safe treatments during this wave of the pandemic. These trial designs, however, need adequate funding as well as scientific leadership, especially as frontline clinicians are tasked with saving lives. In addition, it is important that surrogate outcomes, biomarkers or clinical scales are strongly and directly linked to what matters most for providers and patients, improved chances of recovery from COVID-19.[20,21]

This study provides early evidence of the benefits of global registries to characterize urgent clinical trial research questions now under investigation. Used wisely by active researchers, these registries can help to identify the most promising avenues for developing new therapies, avoid unnecessary duplication, and define unanswered questions that inevitably arise from early research. The registries also constitute a focal point for developing a more comprehensive program to share protocols and research results. Given the early use of pre-prints prior to peer review and multiple journals publishing results, the global research enterprise needs to enlarge and extend the cooperative effort initiated by these registries.

Limitations

Our analysis was limited to a cross-sectional review of trials registered early in the pandemic with one half the studies registered in the previous month. Many of these studies appeared to be exploratory and not explicitly powered to test a specific drug effect on a pre-specified primary endpoint. In addition, our assessment was limited to drugs and plasma, rather than other treatment modalities under

investigation. We did not include trials from Health Canada's Clinical Trials Database because this database does not provide relevant details on trial characteristics. However, if trials are reported in US or WHO database, they are included in our study. We did not apply Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline to evaluate overall quality of clinical trials protocol. Future research can evaluate quality of clinical trials for COVID-19. Finally, our analysis is only as good as the data that it is based on; the International Clinical Trials Registry Platform (ICTRP) gathers information from more than a dozen contributing countries and despite its value, there remain opportunities to improve the consistency and quality of submitted data from both this platform[22] and ClinicalTrials.gov.[23]

CONCLUSIONS

The global pandemic has galvanized the world's research community, and there are signs of remarkable scientific activity.[24] In this review of clinical trials registered early in course of the pandemic's first wave, we found evidence of rapid clinical investigation of existing antivirals, antimalarials, immunosuppressants and oncology treatments for repurposing against COVID-19. Despite this, many registered trials lack features to optimize their scientific value. Global coordination and increased funding of high-quality research may help to maximize scientific progress in rapidly discovering safe and effective treatments.

Table 1. Characteristics of Registered Clinical Trials for SARS-CoV-2 Infection (n=201 trials).

Clinical Trial Characteristics	Total trials (N = 201)
Trial intervention, n (%)	
Drug	188 (93.5)
Plasma	13 (6.5)
Trial registry source, n (%)	
China	100 (49.8)
United States	76 (37.8)
Europe Union	9 (4.5)
Iran	10 (5.0)
Japan	4 (2.0)
ISRCTN	2 (1.0)
Status, n (%)	
Recruiting	120 (59.7)
Not yet recruiting	75 (37.3)
Withdrawn	6 (3.0)
Recruitment country,[a] n (%)	
China	126 (53.9)
Europe	31 (13.3)
Asia (Except China)	18 (7.7)
North America	17 (7.3)
Middle East	13 (5.6)
South America	6 (2.6)
Africa	1 (0.4)
Not reported	22 (9.4)
Phase, n (%)	
0	37 (18.4)
1 or 1/2	5 (2.5)
2	32 (15.9)
2/3	16 (8.0)
3	33 (16.4)
4	51 (24.9)
Not applicable	26 (12.9)
Missing	2 (1.0)
Lead sponsor, n (%)	
Hospitals	111 (55.2)
Industry	36 (17.9)
Government	39 (19.4)
Other[b]	7 (3.5)
Not reported	8 (4.0)

[a]Percentages may exceed 100% as categories not mutually exclusive
[b]Includes foundations and disease trial networks
ISRCTN International Standard Randomised Controlled Trial Number
Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

Table 1 (con't)

Anticipated enrolment, n (%)	
Median (IQR)	100 (50-240)
≤50	54 (26.9)
51-100	53 (26.4)
≥100	94 (46.8)
Outcome,[a] n (%)	
Surrogate/biomarker	85 (42.3)
Clinical scale	33 (16.4)
Clinical outcome	134 (66.7)

Table 2. Products Being Assessed in Registered Clinical Trials for SARS-COV-2 Infection.

Major drug class and drugs	Registered trials, N[a]	Pharmacologic mechanism	Clinical Uses
Antimalarials	**50**		
Chloroquine or hydroxychloroquine	49	Inhibit certain enzymes by interacting with DNA; possible antiviral effect on SARS-CoV through changing the glycosylation of ACE2 receptor and spike protein	Malaria, extraintestinal amebiasis, lupus erythematosus, rheumatoid Arthritis
Dihydroartemisinin/piperaquine	1	Blocks a step in P. falciparum parasite's metabolism needed for its survival	Malaria
Antivirals[b]	**67**		
Asc09/ritonavir	2	HIV-1 protease inhibitor	Investigational drug for HIV (China)
Azvudine	4	Reverse transcriptase inhibitor	Investigational drug for HIV-1
Baloxavir	2	Polymerase acidic (PA) endonuclease inhibitor	Influenza
Danoprevir/ritonavir	4	Danoprevir inhibits hepatitis virus C NS3/4A protease inhibitor;	Investigational drug for Hepatitis C
Darunavir/cobicistat	1	Darunavir inhibits HIV-1 protease enzyme, thus slowing down multiplication of HIV	HIV-1
Favipiravir	11	Inhibits RNA polymerase and prevents replication of the viral genome	Influenza (Japan)
Lopinavir/ritonavir	16	Lopinavir inhibits HIV-1 protease enzyme, thus slowing down multiplication of HIV	HIV-1
Remdesivir	10	Nucleoside analogue; inhibit the action of RNA polymerase; tested for Ebola, MERS, SARS	None; Investigational medicine
Ribavirin	1	Inhibition of viral RNA and protein synthesis	Hepatitis C
Oseltamivir	2	Inhibitor of influenza virus neuraminidase affecting release of viral particles	Influenza
Umifenovir	6	Inhibits membrane fusion in influenza virus	Influenza (Russia and China)
Sofosbuvir/ledipasvir	1	Sofosbuvir inhibits HCV NS5B RNA; ledipasvir inhibits HCV NS5A inhibitor	Hepatitis C
Different antiviral combinations[c]	**7**		
Immunosuppressants	**27**		
Adalimumab	1	Blocks tumor necrosis factor – α, thereby reducing inflammation and other symptoms of the disease	Rheumatoid arthritis, psoriatic arthritis, Juvenile idiopathic arthritis, Crohn's disease, axial spondyloarthritis, Plaque psoriasis
Baricitinib	2	Janus kinase inhibitor	Rheumatoid arthritis
Fingolimod	1	Sphingosine 1-phosphate receptor modulator	Multiple sclerosis
Ixekizumab	1	Interleukin-17A antagonist	Plaque psoriasis, psoriatic arthritis

Leflunomide	1	Pyrimidine synthesis inhibitor	Rheumatoid arthritis, psoriatic arthritis
Pirfenidone	3	Not yet known; reduce fibroblasts production	Idiopathic pulmonary fibrosis
Sarilumab	4	Interleukin-6 receptor antagonist	Rheumatoid arthritis
Thalidomide	2	Not fully known; it has immunomodulatory, antiinflammatory and antiangiogenic properties	Multiple myeloma, erythema nodosum leprosum
Tocilizumab	11	Interleukin-6 receptor antagonist	Rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, cytokine release syndrome
Immunostimulants	**16**		
Interferon	15	Recombinant cytokine with antiviral properties	Hepatitis B, hepatitis C, leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, malignant melanoma
Sargramostim	1	Human granulocyte-macrophage colony-stimulating factor	Acute myeloid leukemia, transplantation
Anticancer drugs	**7**		
Bevacizumab	2	Vascular endothelial growth factor-specific angiogenesis inhibitor	Several types of cancer; for example, colon, lung, breast
Colchicine	2	Tubulin disruption	Gout flare, familial Mediterranean fever
Programmed death receptor-1 (PD-1) antagonists	2	Binds to PD-1 found on T cells, thereby inhibiting T cell proliferation	Several types of cancer; for example, melanoma, lung, kidney
Ruxolitinib	1	Janus kinases inhibitor	Myelofibrosis, polycythaemia vera
Plasma	**14**		
Corticosteroids[i]	**7**		
Dexamethasone	1	Apoptosis of multiple myeloma cells	Multiple myeloma
Methylprednisolone	5	Binds to nuclear receptors to dampen proinflammatory cytokines	Several uses; for example, endocrine, rheumatic and collagen disorders
Immunoglobulins	**3**		Several autoimmune, infectious, and idiopathic diseases
Antithrombotic agents	**3**		
Heparin	2	Inactivation of Factor Xa and Factor IIa	Deep vein thrombosis, pulmonary embolism
Enoxaparin	1		
Antifibrinolytics (Proteinase inhibitors)	**2**		
Camostat	1	Serine protease inhibitor	Chronic pancreatitis, postoperative reflux esophagitis (Japan)
Ulinastat	1	Urinary trypsin inhibitor	Acute pancreatitis, shock (Japan)
Expectorants (Mucolytics)	**2**		
Acetylcysteine	1	Mucolytic agent	Abnormal, viscid, or inspissated mucous secretions
Bromhexine	1	Mucolytic agent	Congestion and cough

Other drugs	**35**		
Aviptadil	1	Analogue of vasoactive intestinal polypeptide	Acute lung injury, sarcoidosis (Europe)
Azithromycin	1	Inhibits bacterial protein synthesis	Mild to moderate infections
Carrimycin	2	Inhibit protein synthesis by binding to ribosomes of the bacteria	Tuberculosis
Camrelizumab	1	Monoclonal antibody; PD-1 inhibitor	Refractory classical Hodgkin lymphoma (China)
CD24Fc	1	Recombinant fusion protein that targets a novel immune pathway checkpoint	Investigational drug
Dexmedetomidine	1	Selective alpha2-adrenergic agonist	Sedation
Escin	2	Inhibition of an inflammatory response at cellular level	Decongestant, reduction of swelling following injuries
GD31 (Nucleoside analog)	1	Nucleoside analogues	Not found
Jakotinib	1	Janus kinase inhibitor	Investigational drug (China)
Losartan	2	Angiotensin II receptor blockers	Hypertension
Meformin	1	Decreases hepatic production and intestinal absorption of glucose, improves insulin sensitivity	Diabetes Mellitus
Meplazumab	1	Humanized anti-CD147 antibody	Investigational drug
Nitric oxide	5	Vasodilating agent	Hypoxic respiratory failure in neonates
Noscapine	1	Opium alkaloid	Cough suppressant
PUL-042	2	Agonists of Toll-like receptors	Investigational drug
Polyinosinic-polycytidylic acid	1	Upregulation of antitumor genes and the induction of cell apoptosis	**Possible anticancer activity**
Recombinant human angiotensin-converting enzyme 2	1	Renin-angiotensin system peptidase	Possible heart failure therapy
Recombinant human interleukin-2	1	T cell growth factor	Melanoma and renal cell carcinoma
Recombinant human granulocyte colony stimulating factor (rhG-CSF)	1	Mediating T cell tolerance	Neutrophil-mediated inflammatory disease
Sildenafil (Urologicals)	1	Sigma receptor agonist activity	Erectile dysfunction
Suramin (Antiprotozoals)	1	Macrofilaricidal	African sleeping sickness and river blindness (Africa)
Thymosin	3	5-Da polypeptide hormone	Investigational drug for cancer
Tranilast	1	Hematopoietic prostaglandin D synthase inhibitor	bronchial asthma, keloid, hypertrophic scar, and allergic disorders (Japan and South Korea)
Triazavirin	1	Guanine nucleotide analogue that inhibits RNA synthesis	Influenza A and B infections (Russia)
Antiviral + Immunosuppressants[d]	**2**		

Antimalarials + Antibacterial[e]	**2**
Antimalarials + Antivirals[f]	**10**
Antivirals + Interferon[g]	**13**
Other combinations[h]	**3**

[a] Column total exceeds 202 as some trials examine multiple drugs; [b] Ritonavir, cobicistat inhibits CYP3A metabolism and increases blood concentration of the other antiviral drug; [c,d,e,f,g,h] Details on drug combinations are provided in Table 3; [i] One trial did not specify type of corticosteroid

Table 3. Drug Combinations Under Investigation for SARS-COV-2 Infection (n=28 combinations).

	Registered trials, N
Different antiviral combinations	7
Asc09f (Asc09/ritonavir) + oseltamivir	1
Darunavir/ritonavir + oseltamivir	1
Favipiravir + lopinavir/ritonavir	1
Lopinavir/ritonavir + oseltamivir	1
Lopinavir/ritonavir + emtritabine/tenofovir	1
Ritonavir + oseltamivir	1
Sofosbuvir + daclatasvir	1
Immunosuppressants combination	
Tocilizumab + adamumab	1
Antiviral + Immunosuppressants	2
Favipiravir + tocilizumab	2
Antimalarials + Antibacterial	2
Hydroxychloroquine + azithromycin	2
Antimalarials + Antivirals	10
Darunavir/cobicistat + hydroxychloroquine	1
Darunavir/ritonavir + favipiravir + chloroquine	1
Darunavir/ritonavir + oseltamivir + chloroquine	1
Favipiravir + chloroquine	2
Hydroxychloroquine + lopinavir or atazanavir/ritonavir	1
Hydroxychloroquine + oseltamivir + lopinavir + interferon	1
Lopinavir/ritonavir + chloroquine	1
Lopinavir/ritonavir + hydroxychloroquine	1
Oseltamivir + chloroquine	1
Antivirals + Interferon	13
Asc09/ritonavir + interferon	1
Favipiravir + interferon	1
Lopinavir/ritonavir + interferon	6
Ribavirin + interferon	2
Ribavirin + lopinavir/ritonavir + interferon	1
Umifenovir + interferon	2
Other combinations	3
Darunavir/cobicistat + thymosin	1
Lopinavir/ritonavir + thymosin	1
Ebastine + interferon + lopinavir	1

Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

A. Contributorship Statement

Hemalkumar B. Mehta (HBM) and G. Caleb Alexander (GCA) conceived the study idea. HBM, Stephan Ehrhardt (SE), Thomas J. Moore (TM), Jodi Segal (JS) and GCA contributed to the study design. HBM performed the data collection and analysis. SE and TM contributed to the data collection. HBM and GCA drafted the first version of the manuscript. HBM, SE, TM, JS and GCA critically reviewed the manuscript and approved the final version.

B. Competing Interests

Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. HBM, SE, TJM and JS have no disclosures to report.

C. Funding

None

D. Data Sharing Statement

Data is stored in an open-access Google Sheet document - https://docs.google.com/spreadsheets/d/1p_229olyi7ft6MCLYXdS4-dkKszjnAiSnLRVO68OLk8/edit#gid=0

E. Acknowledgements

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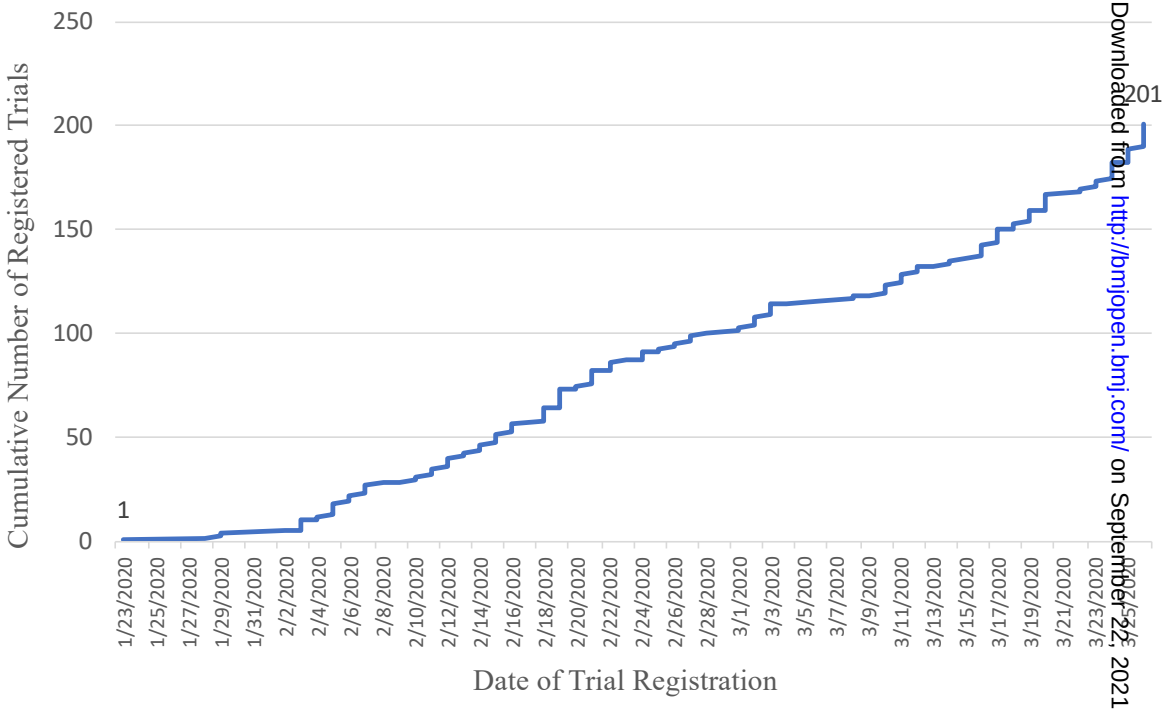
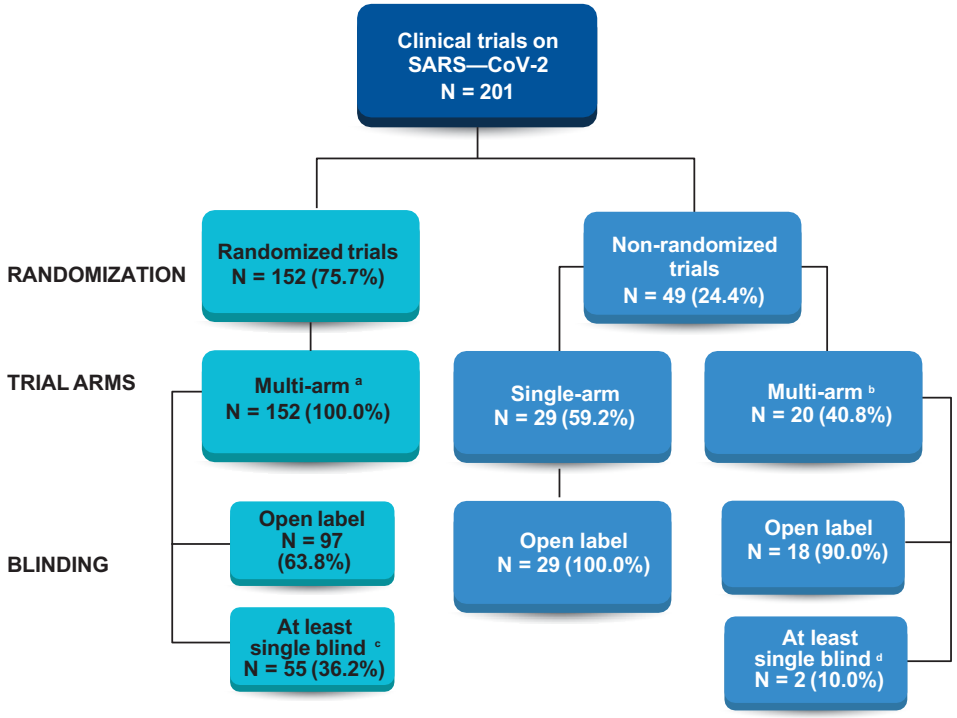
Figure 1. Cumulative Number of Registered Clinical Trials of Products for SARS-CoV-2 Infection.



Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

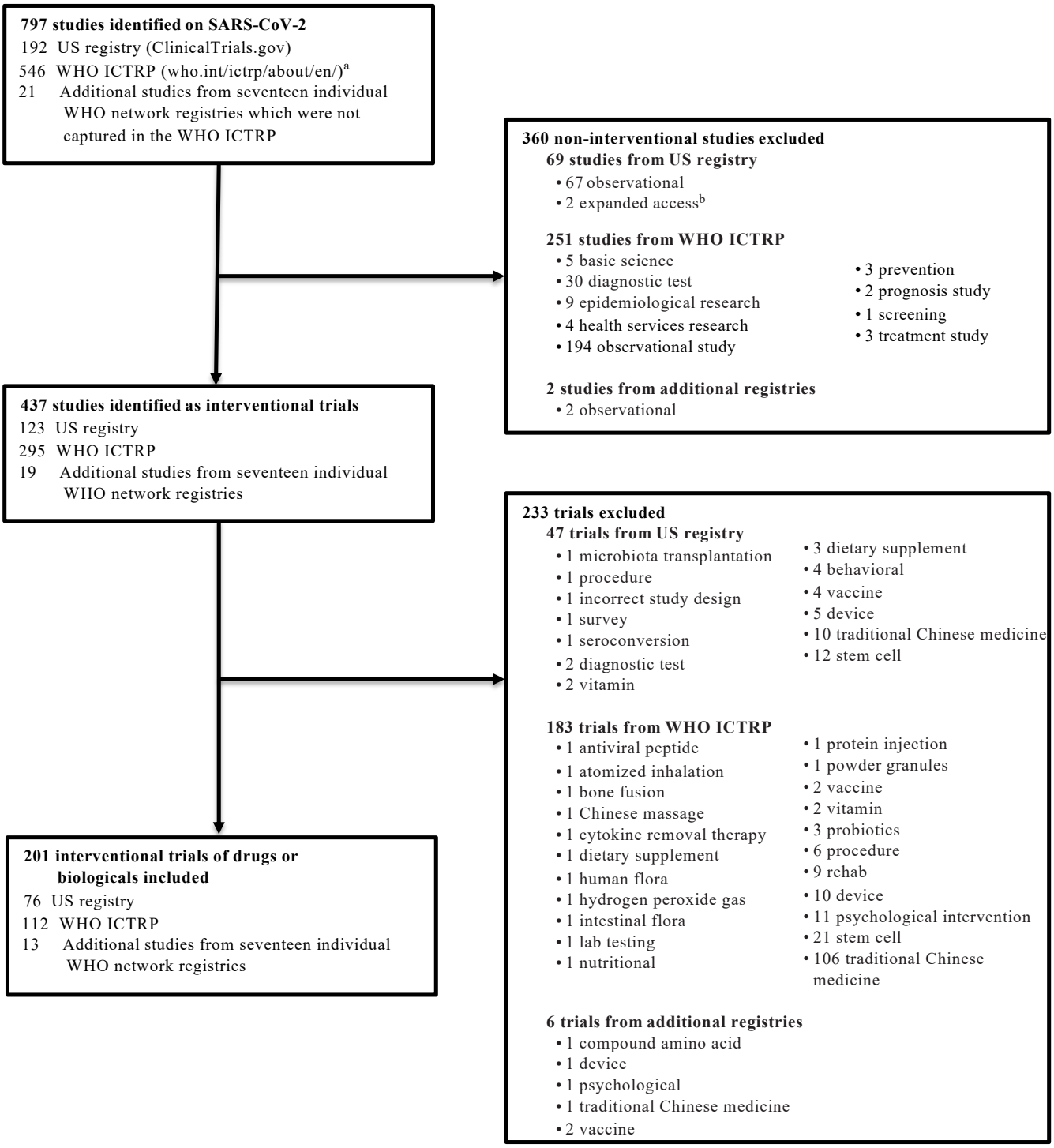
Figure 2. Study Designs of Registered Clinical Trials of Products for SARS-CoV-2 Infection (N=201 trials).



[a] Includes 147 parallel, 1 platform and 4 sequential trials; [b] Includes 1 crossover, 1 factorial, 17 parallel and 1 historical control arm trials; [c] Includes 14 single, 5 at least single, 16 double, 2 triple and 18 quadruple blinded trials; [d] Includes 2 double blind trials

Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

eFigure 1. Study Selection Flowchart



ICTRP International Clinical Trials Registry Platform; **WHO** World Health Organization

[a] To avoid double counting we excluded 121 studies which were originally registered in the US registry

[b] Expanded access refers to study designs where investigational drugs are provided to patients who cannot participate in clinical trial

Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

eTable 1. Search Strategy.

Search strategy	"COVID-19" OR "COVID 19" OR "COVID19" OR "COVID2019" OR "COVID 2019" OR "COVID-2019" OR "novel coronavirus" OR "new coronavirus" OR "novel corona virus" OR "new corona virus" OR "SARS-CoV-2" OR "SARSCoV2" OR "SARS-CoV2" OR "2019nCoV" OR "2019-nCoV" OR "2019 coronavirus" OR "2019 corona virus" OR "coronavirus disease 2019" OR "severe acute respiratory syndrome coronavirus 2" OR "sars-coronavirus-2" OR "coronavirus disease 2019" OR "corona virus disease 2019"

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, eFigure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, 8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9, 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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