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CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19

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4	$\frac{2}{3}$	CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS
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26 27	22	Support
28	23	None
29	24	
30	25	Disclosure
31	26	Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; has
32 33	27 28	served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics,
34	28 29	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
35	29 30	reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.
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47 ABSTRACT

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

51 Design, setting and participants. Cross-sectional analysis of clinical trials for the treatment of 52 COVID-19 that were registered in the United States or in countries contributing to the World Health 53 Organization's International Clinical Trials Registry Platform (ICTR). Relevant trial entries of drugs 54 or plasma were downloaded on March 26, 2020, de-duplicated, verified with reviews of major medical 55 journals and World Health Organization websites and independently analyzed by two reviewers.

¹⁹ 56 **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 for beet terien only

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2 3	85	INTRODUCTION
4	86	Since its identification in China in late 2019, the epidemic of severe acute respiratory syndrome
5 6	87	coronavirus 2 (SARS-CoV-2) has spread rapidly, with 206 countries and territories reporting cases by
7 8	88	April 2020.1 Although knowledge of the coronavirus disease 2019 (COVID-19) pandemic's true
9	89	epidemiology has been constrained by the limited availability of testing and surveillance, as of April 1,
10 11	90	2020 nearly one million cases had been confirmed around the world, with over 46,000 deaths and the
12 13	91	number of new cases doubling as frequently as every few days. ²
14	92	
15 16	93	The impact of the pandemic, as well as uncertainty regarding its future course, has unleashed a wave of
17 18	94	biomedical research to identify safe and effective treatments for COVID-19. While new molecular
19 20	95	entities are under investigation, many therapies previously approved by regulators for the treatment of
21	96	other diseases are also being evaluated for repurposing for viral suppression or for lessening the
22 23	97	inflammatory consequences of infection. ³ There is also interest in assessing the use of convalescent
24 25	98	plasma to treat COVID-19.4
26	99	
27 28	100	Both media ⁵ and industry ^{6,7} reports have characterized products being assessed for therapeutic activity
29 30	101	against COVID-19. We sought to complement these with a rigorous appraisal of early efforts around
31 32	102	the world to identify safe and efficacious treatments to address the pandemic. In addition to identifying
	103	investigational therapies, we also characterized the sponsorship, critical design elements and specified
35	104	outcomes of each registered clinical trial. While our analysis represents an early snapshot of a
	105	continually evolving area, it nevertheless provides timely and globally important information for
38 39	106	researchers, policy-makers and the general public.
40	107	
41 42	108 109	METHODS
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44 45	110	Data Sources
46	111	We used information from the World Health Organization's (WHO) clinical trials registry network and
40	112	ClinicalTrials.gov. ClinicalTrials.gov is a registry of public and privately funded clinical trials
49 50	113	conducted around the world maintained by the United States (U.S.) National Library of Medicine on
51	114	behalf of the National Institutes of Medicine. The WHO registry network includes clinical trials from
	115	countries including Australia, Brazil, China, South Korea, India, Cuba, European Union, Germany,
54 55	116	Iran, Japan, Lebanon, Thailand, Netherlands, Pan Africa, Peru, Sri Lanka and the United Kingdom.
	117	Each participating country sends their data to the International Clinical Trials Registry Platform

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(ICTRP) maintained by the WHO.⁸ Both the WHO registry⁹ and ClinicalTrials.gov¹⁰ require that 2 118 registered trials meet specific criteria for content, quality and validity, accessibility, unique 119

120 identification, technical capacity and administration, and requirements of the International Committee 121 of Medical Journal Editors.

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10 11 123 **Registry Searches**

12 124 We downloaded all COVID-19 trials provided by the WHO in a Microsoft Excel spread sheet.¹¹ The 13 14 125 WHO curated all COVID-19 trials published on the ICTRP database in an excel file. Therefore, no 15 search strategy was applied to the ICTRP database. We also performed a manual search of each of the 16 126 17 18 127 WHO's seventeen network registries, such as EU Clinical trials register to identify additional trials, ¹⁹ 128 vielding 21 additional studies. We combined these data with information from the ClincialTrials.gov 20 21 1 29 registry.¹² All searches were last updated on March 26, 2020. To identify trials registered in the U.S., 22 23 130 we searched the ClinicalTrials.gov registry for trials related to the 2019 novel coronavirus using ²⁴ 131 keywords "Coronavirus" or "COVID-19" or "COVID19" or "2019 novel coronavirus" or "2019-26 132 nCoV" or "SARS-CoV-2" (eTable 1). In order to assess whether there were omitted trials, we also 27 searched major medical journals, such as Lancet, New England Journal of Medicine and JAMA, and 28 1 3 3 29 ²⁹₃₀134 websites from the World Health Organization, U.S. Centers for Disease Control and Prevention and ³¹ 135 32 media aggregators. These searches did not reveal any additional trials to be included in the analysis.

34 For each product that that was approved by regulators, we searched for information from the European 35 137 ³⁶ 37 138 Medicines Agency (EMA)¹³ and U.S. Food and Drug Administration (FDA)¹⁴ describing mechanisms ³⁸ 139 39 of action and approved indications. We searched the pharmaceutical manufacturers' websites and other 40 140 online sources for information about drugs that were not approved in the European Union or the United 41 42 141 States.

45 143 **Trial Selection**

We included all studies conducted on patients diagnosed with COVID-19. First, we selected 47 144 48 49 145 interventional clinical trials based on the "study type" variable (eFigure 1). This variable contains ⁵⁰ 146 values such as interventional trials, observational studies, expanded access, diagnostic test, basic 51 52 147 science, prevention, prognosis, epidemiological research, health services research and screening. 53 54 148 Interventional studies are "studies that prospectively assign human participants or groups of humans to 56 149 55 one or more health-related interventions to evaluate the effects on health outcomes".^{15,16} To be

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150 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 151 152 standardized information about the components of each intervention, two individuals (KM, HM) 153 independently reviewed each interventional study to identify any trials of a drug or plasma. Any 154 disagreement was resolved by a third reviewer (GCA). Because study focus was on evaluating drugs 10 11 155 or plasma treatments, we excluded trials of stem cell transplants, devices, diagnostic tests, traditional 12 156 Chinese medicines/herbal medicine, rehabilitation, dietary supplements and psychological 13 14 157 interventions. We did not limit any studies based on the outcomes they evaluated. We also excluded 15 16 158 one trial with implausible information regarding its study design (a single-arm randomized controlled 17 18 159 trial).

21 161 Data extraction and management

23 162 We extracted the following information from each trial: unique trial number; trial registry source ²⁴ 163 (WHO network registry country or the U.S.), registration date, recruitment status (recruiting, not yet 26 164 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), 28 165 ²₃₀ 166 intervention model (single-arm, parallel, cross-over, factorial, platform trial, sequential), blinding ³¹ 167 32 (open, single, double, triple, quadruple,), primary outcome (surrogate/biomarker, clinical scale, clinical 33 168 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 35 169 ³⁶ 37 170 site that can potentially enroll participants) to identify recruitment countries. Enrolment number ³⁸ 171 39 reflects the estimated total number of participants to be enrolled or the actual total number of 40 172 participants enrolled.

174 We used the primary sponsor and collaborators fields from the U.S. registry, and primary and ⁴⁵ 175 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 47 176 48 49 177 primary sponsor was a pharmaceutical company, or a known funding body like the National Institutes ⁵⁰ 178 of Health (NIH) was neither a primary sponsor or collaborators/secondary sponsor, and at least one 52 179 collaborator was a pharmaceutical company; (ii) the lead sponsor was a known government research 54 180 funding agency if identified as such or at least one collaborator was this funder; (iii) the lead sponsor 56 181 was a hospital if so stated; (iv) all others were classifies as other. For some trials, the study design or

182 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 183 184 (n=37), we used the following rules to assign intervention model and blinding: (i) trials with a single 185 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 186 11 187 was not reported and could not be inferred. We grouped parallel, cross-over, factorial, platform, and 188 sequential intervention trials as multi-arm (>2 trial arms).

16 190 Two reviewers (HM, TM) independently reviewed primary outcomes of all trials and assigned them as ¦' 191 surrogate or biomarker, clinical scale, or clinical outcomes. Surrogate or biomarker included any ¹⁹ 192 measure of SARS-Cov-2 or any blood test; clinical scales included measures of oxygenation, 21 193 Sequential Organ Failure Assessment (SOFA) score, National Early Warning Score 2 (NEWS2) score, 23 194 lung injury score or any measure of pulmonary harms; and clinical outcomes included symptoms, ²⁴ 195 clinical improvement scores, intubation, hospitalization or death. Reviewer disagreement was resolved 26 196 by discussion and consensus.

29 30 198 We identified drugs under investigation for COVID-19 from the experimental and/or control arm of ³¹ 199 each trial, including multiple drugs when they were studied in combination. Because the trial registries 33 200 did not record drugs in a standardized format, two pharmacist reviewers (HM, SS) independently 35 201 extracted this information, converting brand names were scientific names and correcting minor spelling $^{36}_{37}202$ errors. We used the WHO's Anatomical Therapeutic Chemical Classification System to classify drugs ³⁸ 203 in major therapeutic or pharmacological subgroups. For the 18 drugs (e.g., remdesivir) that were not 40 204 included in the WHO's ATC algorithms, we used product information from the European Medicines 42 205 Agency, U.S. FDA or the companies' websites to characterize the product.

45 207 Analysis

We used descriptive statistics to analyze the extracted data. We summarized the characteristics of all 47 208 48 49 209 included trials using frequency and percentages. We listed unique drugs under investigation and the ⁵⁰ 210 number of registered clinical trials for each product. We plotted the number of cumulative trials by 51 52 211 their registration date. All data was extracted and stored in an open-access Google Sheet document 53 54 212 (Link). The study was considered non-human subject research by the Johns Hopkins University ⁵⁵₅₆ 213 Institutional Review Board. We used SAS version 9.4 (SAS Institute Inc.) for all analyses.

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³ 4 215	Patient and public involvement
5 216 6 217 8 218 9 219 10 220	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
12 221	Characteristics of Clinical Trials
$^{13}_{14}222$	Overall 201 clinical trials were registered for testing the therapeutic benefits of 156 drugs or plasma,
¹⁵ 223 16	including 62 in monotherapy and 92 different combinations (Table 1). Although the trials were
17 224	initiated in more than 17 countries or regions, 100 (49.8%) were registered in China, and 78 (37.8%) in
18 19 225	the U.S. Of the 201 trials, 4 (2.0%) were registered in January 2020, 97 (48.2%) in February and 100
$\frac{20}{21}226$	(49.8%) between March 1 st and March 26, 2020 (Figure 1). Nearly 60% of the trials were recruiting
22 227 23	patients, and more than half were sponsored by hospitals or universities (55.2%), while about one in
24 228	five were sponsored by a government (19.4%) and a similar proportion (17.9%) were industry
²⁵ 26 229	sponsored.
²⁷ 230	
29 231	In 152 trials (75.7%) patients were randomized to treatment or comparator, including 55 trials with
30 31 232	some form of blinding and 97 open label studies (Figure 2). The 49 (24.4%) of trials without a
$\frac{32}{33}233$	randomized design included 29 single armed studies, and 20 trials with some comparison group. Of
³⁴ 234 35	the 201 trials, 54 (26.9%) were parallel group, randomized controlled trials with at least single-
36 235	blinding.
37 38 236	
³⁹ ₄₀ 237	Primary Endpoints
41 238 42	Most trial designs featured multiple endpoints. Clinical endpoints were identified in 134 (66.7%) of
43 239	trials and included COVID-19 symptoms, death, recovery, required intensive care and hospital
$\frac{44}{45}$ 240	discharge. Clinical scales were being used in 33 (16.4%) trials, most often measures of oxygenation
46 47 241	and critical illness assessment instruments. Surrogate endpoints or biomarkers were studied in 88
48 242	(42.3%) of trials, primarily assays of viral load. None of the trials assessed patient and public
49 50 243	involvement or quality of life as outcome measures.
⁵¹ 52 244	
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55 246	Study Size
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247 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 248

249 enroll 100 or more patients, with 20 (9.6%) studies anticipating enrollment of 500 or more patients.

8 251 9 **Therapies Under Evaluation**

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11 252 Overall 92 drugs or plasma were under investigation, including 64 in monotherapy and 28 different ¹² 253 combinations (Table 2). Only 8 (5.1%) products or combinations involved new molecular entities. The 14 2 5 4 other test therapies had a wide range of prior medical uses; 412 (18.8%) were antivirals, 9 (14.1%) 16 255 immunosuppressants other than corticosteroids, 4 anticancer drugs (6.3%) 3 (4.7%) antimalarials, 2 $^{17}_{18}256$ (3.1%) corticosteroids, 2 (3.1%) immunostimulants and 2 (3.1%) antithrombotic agents. The 28 ¹⁹ 257 different combinations including antivirals, antimalarials, immunosuppressants, immunostimulants and 21 258 antibacterials (Table 3). Of these, nine (32%) were antimalarial/antiviral combinations, seven (25%) 22 23 259 antiviral/immunosuppressant combination and six (21%) antiviral/interferon combination.

²⁴ 260 25 261 26 261 27 262 **DISCUSSION**

²⁸ 263 This study characterized the scope, objectives, and content of the current global research program to 30 264 find effective therapies for COVID-19 as reported to the leading clinical trial registries. These data 32 265 show that the primary focus of clinical trial research at present is assess whether a wide range of ₃₄ 266 existing therapeutic products might also be effective against acute illnesses caused by the novel SARS-³⁵ 267 Cov-2 virus. Because one-third of trials exclude clinical endpoints, nearly one half are designed to 37 268 enroll fewer than 100 patients and two-thirds are open label, many of these studies are likely to yield 39 269 only preliminary evidence of a given treatment's safety and effectiveness against COVID-19. 40 41 270

42 271 Our results indicate that current scientific activity is concentrated in China and the United States, 43 44 272 accounting for 87.6% of the studies. Some of the products under investigation, such as remdesivir, have 45 46 273 considerable pre-clinical and clinical evidence to support their potential value. In addition to single site 47 48 274 trials, several major, multi-site trials of therapies against COVID-19 are also underway. Solidarity, ⁴⁹ 275 announced by the World Health Organization on March 20, 2020, is a multi-center, adaptive, 50 51 276 randomized, open-label, five arm trial testing remdesivir, chloroquine/hydroxychloroquine, 52 53 277 ritonavir/lopinavir and ritonavir/lopinavir with interferon-beta against standard of care in dozens of ⁵⁴ 278 countries around the globe.¹⁸ Discovery, coordinated by France's National Institute of Health and 56 279 Medical Research (Inserm), is designed as an add-on trial in Europe and will study the same drugs with 57

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

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

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

mitations

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

2 312 analysis is only as good as the data that it is based on; the International Clinical Trials Registry 4 313 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 platform²² and ClinicalTrials.gov.²³

10 3 1 7 **CONCLUSIONS**

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The global pandemic has galvanized the world's research community, and there are signs of 12 318 14 319 remarkable scientific activity.²⁴ In this review of clinical trials registered early in course of the 15 320 16 pandemic's first wave, we found evidence of rapid clinical investigation of existing antivirals, 17 321 antimalarials, immunosuppressants and oncology treatments for repurposing against COVID-19. 19 322 Despite this, many registered trials lack features to optimize their scientific value. Global coordination ²⁰₂₁ 323 resea. .ents and increased funding of high-quality research may help to maximize scientific progress in rapidly 22 324 discovering safe and effective treatments.

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3 4 326	The authors gratefully acknowledge Kristin Meek, Matthew Tajanlangit and Jamie Heyward for
5 6 327	assistance extracting information from trial registries and Sneha Sura for assistance reviewing drug
7 328 8	information and data management.
9 329	
10 11 330	It was not appropriate or possible to involve patients or the public in the design, or conduct, or
12 331 13	reporting, or dissemination plans of our research.
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Clinical Trial Characteristics	Total trials ($N = 201$)
Trial intervention, n (%)	
Drug	188 (93.5)
Plasma	13 (6.5)
Trial registry source, n (%)	X
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 (%)	2 (1.0)
Recruiting	120 (59.7)
Not yet recruiting	75 (37.3)
Withdrawn	6 (3.0)
Recruitment country, ^a n (%)	0 (3.0)
China	126 (52 0)
	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 categor	
^b Includes foundations and disease trial net	
ISRCTN International Standard Randomi	
Sources: World Health Organization and G	ClinicalTrials.gov (as of March 26, 2020
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² 337 **Table 1.** Characteristics of Registered Clinical Trials for SARS-CoV-2 Infection (n=201 trials).

2	339	Table 1 (con't)
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3 340		
4	Anticipated enrolment, n (%)	
5	Median (IQR)	100 (50-240)
6 7	<u></u>	54 (26.9)
8	51-100	53 (26.4)
9	≥100	94 (46.8)
10	Outcome, ^a n (%)	
11	Surrogate/biomarker	85 (42.3)
12 13	Clinical scale	33 (16.4)
13	Clinical outcome	134 (66 7)
15 341		
16 342		
$17 343 \\18 244$		
18 344 19 344		
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 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	Malaria, extraintestinal amebiasis, lupu
		DNA; possible antiviral effect on SARS-CoV	erythematosus, rheumatoid Arthritis
		through changing the glycosylation of ACE2	
		receptor and spike protein	
Dihydroartemisinin/piperaquine		Blocks a step in P. falciparum parasite's	Malaria
	<u> </u>	metabolism needed for its survival	
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 inhibits hepatitis virus C NS3/4A	Investigational drug for Hepatitis C
Danoprevir/ritonavir	4	protease inhibitor;	
		Darunavir inhibits HIV-1 protease enzyme, thus	HIV-1
Darunavir/cobicistat	1	slowing down multiplication of HIV	
		Inhibits RNA polymerase and prevents	Influenza (Japan)
Favipiravir	11	replication of the viral genome	
		Lopinavir inhibits HIV-1 protease enzyme, thus	HIV-1
Lopinavir/ritonavir	16	slowing down multiplication of HIV	
		Nucleoside analogue; inhibit the action of RNA	None; investigational medicine
Remdesivir	10	polymerase; tested for Ebola, MERS, SARS	
Ribavirin	1	Inhibition of viral RNA and protein synthesis	Hepatitis C
		Inhibitor of influenza virus neuraminidase	Influenza
Oseltamivir	2	affecting release of viral particles	
Umifenovir	6	Inhibits membrane fusion in influenza virus	Influenza (Russia and China)
		Sofosbuvir inhibits HCV NS5B RNA; ledipasvir	Hepatitis C
Sofosbuvir/ledipasvir	1	inhibits HCV NS5A inhibitor	
Different antiviral combinations ^c	7		
Immunosuppressants	27		
		Blocks tumor necrosis factor – α , thereby	Rheumatoid arthritis, psoriatic arthritis
		reducing inflammation and other symptoms of	Juvenile idiopathic arthritis, Crohn's
		the disease	disease, axial spondyloarthritis, Plaque
Adalimumab	1		psoriasis
Denieitinih	2	Janus kinase inhibitor	Rheumatoid arthritis
Baricitinib	1	Sphingosine 1-phosphate receptor modulator	Multiple sclerosis
Fingolimod	1		

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
	-	Not fully known, it has immunomodulatory,	Multiple myeloma, erythema nodosum
Thalidomide	2	antiinflammatory and antiangiogenic properties	leprosum
		Interleukin-6 receptor antagonist	Rheumatoid arthritis, giant cell arteritis,
Tocilizumab	11		juvenile idiopathic arthritis, cytokine release syndrome
Immunostimulants	16		
	10	Recombinant cytokine with antiviral properties	Hepatitis B, hepatitis C, leukaemia,
		recombinant of toxine with and that properties	multiple myeloma, follicular lymphoma,
Interferon	15		carcinoid tumour, malignant melanoma
		Human granulocyte-macrophage colony-	Acute myeloid leukemia, transplantation
Sargramostim	1	stimulating factor	
Anticancer drugs	7		
		Vascular endothelial growth factor-specific	Several types of cancer; for example,
Bevacizumab	2	angiogenesis inhibitor	colon, lung, breast
Colchicine	2	Tubulin disruption	Gout flare, familial Mediterranean fever
Programmed death receptor-1 (PD-1)		Binds to PD-1 found on T cells, thereby	Several types of cancer; for example,
antagonists	2	inhibiting T cell proliferation	melanoma, lung, kidney
Ruxolitinib	<u> </u>	Janus kinases inhibitor	Myelofibrosis, polycythaemia vera
Plasma	14		
Dexamethasone	1	Apoptosis of multiple myeloma cells	Multiple myeloma
	1	Binds to nuclear receptors to dampen	Several uses; for example, endocrine,
Methylprednisolone	5	proinflammatory cytokines	rheumatic and collagen disorders
			Several autoimmune, infectious, and
Immunoglobulins	3		idiopathic diseases
Antithrombotic agents	3		
Heparin	2	—— Inactivation of Factor Xa and Factor IIa	Deep vein thrombosis, pulmonary
Enoxaparin	1		embolism
Antifibrinolytics (Proteinase inhibitors)	2	0.1	
	1	Serine protease inhibitor	Chronic pancreatitis, postoperative reflu
Camostat	<u> </u>	Urinory tryngin inhibitor	esophagitis (Japan)
Ulinastat Expectorants (Mucolytics)	2	Urinary trypsin inhibitor	Acute pancreatitis, shock (Japan)
Expectorants (Mucorytics)	4	Mucolytic agent	Abnormal, viscid, or inspissated mucous
Acetylcysteine	1	muony no ugont	secretions
Bromhexine	1	Mucolytic agent	Congestion and cough
			6 6
			Page 16 of 22
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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
		Inhibit protein synthesis by binding to ribosomes	Tuberculosis
Carrimycin	2	of the bacteria	
Camrelizumab	1	Monoclonal antibody; PD-1 inhibitor	Refractory classical Hodgkin lymphome (China)
		Recombinant fusion protein that targets a novel	Investigational drug
CD24Fc	1	immune pathway checkpoint	
Dexmedetomidine	1	Selective alpha2-adrenergic agonist	Sedation
		Inhibition of an inflammatory response at	Decongestant, reduction of swelling
Escin	2	cellular level	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
		Decreases hepatic production and intestinal	Diabetes Mellitus
		absorption of glucose, improves insulin	
Meformin	1	sensitivity	
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
		Upregulation of antitumor genes and the	Possible anticancer activity
Polyinosinic-polycytidylic acid	1	induction of cell apoptosis	
Recombinant human angiotensin-converting		Renin-angiotensin system peptidase	Possible heart failure therapy
enzyme 2	1		
Recombinant human interleukin-2	1	T cell growth factor	Melanoma and renal cell carcinoma
Recombinant human granulocyte colony		Mediating T cell tolerance	Neutrophil-mediated inflammatory
stimulating factor (rhG-CSF)	1		disease
Sildenafil (Urologicals)	1	Sigma receptor agonist activity	Erectile dysfunction
		Macrofilaricidal	African sleeping sickness and river
Suramin (Antiprotozoals)	1		blindness (Africa)
Thymosin	3	5-Da polypeptide hormone	Investigational drug for cancer
		Hematopoietic prostaglandin D synthase inhibitor	bronchial asthma, keloid, hypertrophic scar, and allergic disorders (Japan and
Tranilast	1		South Korea)
m · · ·		Guanine nucleotide analogue that inhibits RNA	Influenza A and B infections (Russia)
Triazavirin	1	synthesis	
Antiviral + Immunosuppressants ^d	2		
			Page 17 of 2 2
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1			
2	Antimalarials + Antibacterial ^e	2	
3	Antimalarials + Antivirals ^f	10	
4	Antivirals + Interferon ^g	13	
5	Other combinations ^h	3	
6			

^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; ⁱOne trial did not specify type of corticosteroid For peer review only

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

	Registered trials,
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.
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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"

REFERENCES

¹ World Health Organization Dashboard. Available at:

https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd (Accessed April 2, 2020).

² Coronavirus Resource Center. Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering. Available at: <u>https://coronavirus.jhu.edu/data/new-cases</u> (Accessed April 2, 2020).

³ Harrison C. Coronavirus puts drug repurposing on the fast track. Nature Biotechnology. February 27, 2020. Available at: <u>https://www.nature.com/articles/d41587-020-00003-1</u> (Accessed April 2, 2020).

⁴ Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. Published online March 27, 2020. doi:10.1001/jama.2020.4783

⁵ Zimmer C. Scientists Identify 69 Drugs To Test Against the Coronavirus. New York Times. March 22, 2020. Available at: <u>https://www.nytimes.com/2020/03/22/science/coronavirus-drugs-chloroquine.html</u> (Accessed March 25, 2020).

⁶ The Milken Institute. COVID-19 Treatment and Vaccine Tracker. Available at: <u>https://milkeninstitute.org/sites/default/files/2020-03/Covid19-Tracker-3-36-20-FINAL.pdf</u> (Accessed March 25, 2020).

⁷ Garde D. An Updated Guide to the Coronavirus Drugs and Vaccines in Development. STAT News. Available at: <u>https://www.statnews.com/2020/03/19/an-updated-guide-to-the-coronavirus-drugs-and-vaccines-in-development/</u> (Accessed March 26, 2020).

⁸ International Clinical Trials Registry Platform (ICTRP). World Health Organization. Available at: <u>https://www.who.int/ictrp/network/primary/en/</u> (Accessed March 26, 2020).

⁹ World Health Organization Data Set. International Clinical Trials Registry Platform (ICTRP). Available at: <u>https://www.who.int/ictrp/network/trds/en/</u> (Accessed March 25, 2020).

¹⁰ ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies. National Library of Medicine. Available at:
 <u>https://prsinfo.clinicaltrials.gov/definitions.html</u> (Accessed March 25, 2020).

¹¹ World Health Organization Database of COVID-19 Trials. Available at: who.int/ictrp/en/ (Accessed March 25, 2020).

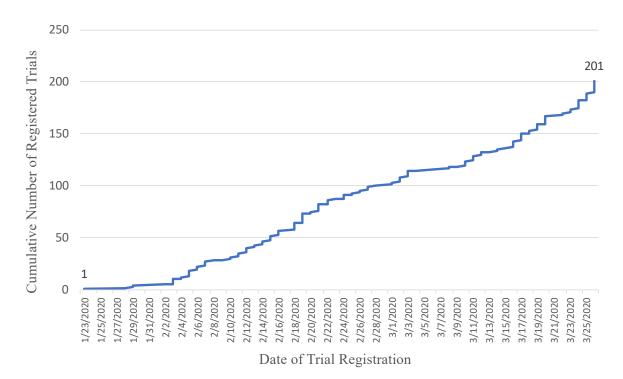
¹² ClinicalTrials.gov. National Library of Medicine. Available at: <u>www.clinicaltrials.gov</u> (Accessed March 25, 2020).

¹³ European Medicines Agency. Available at: <u>https://www.ema.europa.eu/en</u> (Accessed March 25, 2020).

¹⁴ U.S. Food and Drug Administration. Available at: FDA.gov (Accessed March 25, 2020).

	Trial Registries. World Health Organization. Available at: hdle/10665/76705/9789241504294 eng.pdf;jsessionid=719FA2F
AFABCE205F4CD68277AD9FEAD	?sequence=1 (Accessed March 25, 2020).
e e	ation Data Element Definitions for Interventional and
Observational Studies. ClinicalTrials	s.gov. March 7, 2019. Available at:
https://prsinfo.clinicaltrials.gov/defin	itions.html (Accessed March 25, 2020).
	Sherman RE, Aberle LH, Tasneem A. Characteristics of Clinical
Trials Registered in ClinicalTrials.go	v, 2007-2010. JAMA. 2012;307:1838–1847.
	'solidarity trial' to jumpstart search for COVID-19 treatment."
UN News. March 18, 2020. Availab April 3, 2020).	le at: https://news.un.org/en/story/2020/03/1059722 (Accessed
April 3, 2020).	
	launches global megatrial of the four most promising coronavirus
	Available at: <u>https://www.sciencemag.org/news/2020/03/who-</u>
launches-global-megatrial-four-most-	promising-coronavirus-treatments (Accessed April 3, 2020).
20 Sallack MI Sonthil M Wall ND	Making Magningful Clinical Use of Diamarkars Diamark
Insights. 2017;12:1-7.	Making Meaningful Clinical Use of Biomarkers. Biomark
məigniə. 2017,12.1-7.	
²¹ Pletcher MJ Pignone M Evaluatin	g the clinical utility of a biomarker: a review of methods for
estimating health impact. Circulation	
²² Viergever RF, Karam G, Reis A, G	hersi D. The quality of registration of clinical trials: still a
problem. PLoS One. 2014;9:e84727.	
23 Tao T. Fain KM. Zarin DA. How to	a word common problems when using ClinicalTrials gov in
research: 10 issues to consider. BMJ.	avoid common problems when using ClinicalTrials.gov in
research. To issues to consider. Divij.	2018,501.K1452
²⁴ Apuzzo M, Kirkpatrick DD. Covid	I-19 Changed How the World Does Science, Together. New York
Times. April 1, 2020. Available at:	https://www.nytimes.com/2020/04/01/world/europe/coronavirus-
science-research-cooperation.html	
(Accessed April 1, 2020).	
	Page 22 of 22

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

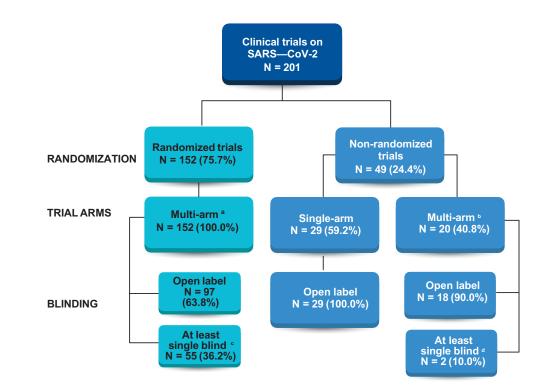


Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

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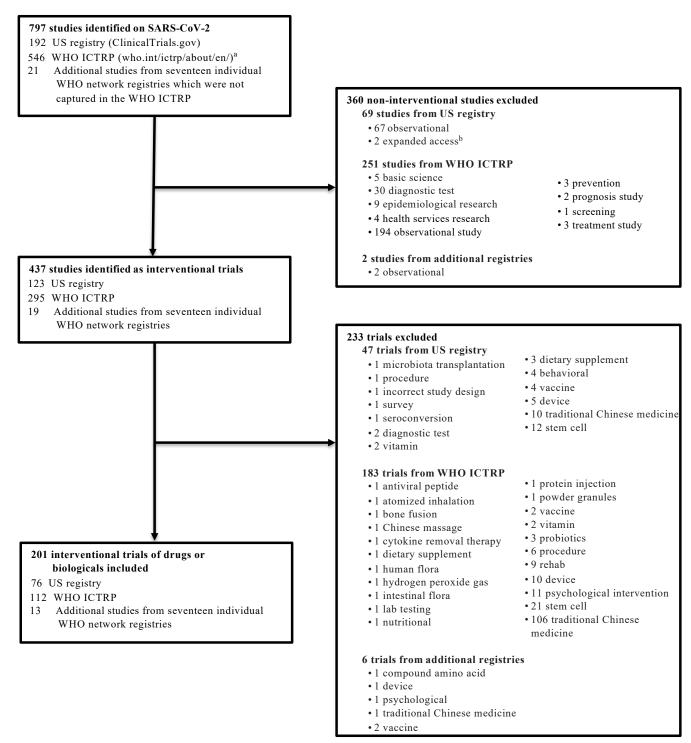
Figure 2. Study Designs of Registered Clinical Trials of Products for SARS-CoV-2 Infection (N=201 trials).



^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)

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eFigure 1. Study Selection Flowchart



ICTRP International Clinical Trials Registry Platform; WHO World Health Organization

^aTo 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
B 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 metavanalysis. http://bmjopen.bmj.com/site/about/guidelines.xhtml	7

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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		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

41 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.
42 doi:10.1371/journal.pmed1000097

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CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19

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Manuscript ID	bmjopen-2020-039978.R1
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Complete List of Authors:	Mehta, Hemalkumar; Johns Hopkins University Bloomberg School of Public Health, Epidmeiology Ehrhardt, Stephan ; Johns Hopkins University, Department of Epidemiology Moore, Thomas ; Institute for Safe Medication Practices, Segal, Jodi; Johns Hopkins University Bloomberg School of Public Health, Alexander, G Caleb; Johns Hopkins University, Epidemiology
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Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, INFECTIOUS DISEASES





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4	$\frac{2}{3}$	CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS
5	4	FOR COVID-19
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7 8	6	
9	7	Hemalkumar B. Mehta, PhD ^{1,2}
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24	20	5. Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
25	21	
26 27	22	Support
28	23	None
29	24	
30	25	Disclosure
31	26	Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; has
32 33	27 28	served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics,
34	28 29	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
35	29 30	reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.
36	31	HBM, SE, TJM and JS have no disclosures to report.
37	32	
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47 ABSTRACT

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

51 Design, setting and participants. Cross-sectional analysis of clinical trials for the treatment of 52 COVID-19 that were registered in the United States or in countries contributing to the World Health 53 Organization's International Clinical Trials Registry Platform (ICTR). Relevant trial entries of drugs 54 or plasma were downloaded on March 26, 2020, de-duplicated, verified with reviews of major medical 55 journals and World Health Organization websites and independently analyzed by two reviewers.

¹⁹ 56 **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 for beer terien only

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1 2	05	
2 3 4 5	85	INTRODUCTION
	86	Since its identification in China in late 2019, the epidemic of severe acute respiratory syndrome
6	87	coronavirus 2 (SARS-CoV-2) has spread rapidly, with 206 countries and territories reporting cases by
7 8	88	April 2020.1 Although knowledge of the coronavirus disease 2019 (COVID-19) pandemic's true
9	89	epidemiology has been constrained by the limited availability of testing and surveillance, as of April 1,
10 11	90	2020 nearly one million cases had been confirmed around the world, with over 46,000 deaths and the
12 13	91	number of new cases doubling as frequently as every few days. ²
14	92	
15 16	93	The impact of the pandemic, as well as uncertainty regarding its future course, has unleashed a wave of
17 18	94	biomedical research to identify safe and effective treatments for COVID-19. While new molecular
19	95	entities are under investigation, many therapies previously approved by regulators for the treatment of
20 21	96	other diseases are also being evaluated for repurposing for viral suppression or for lessening the
22 23	97	inflammatory consequences of infection. ³ There is also interest in assessing the use of convalescent
24	98	plasma to treat COVID-19.4
25 26	99	
27	100	Both media ⁵ and industry ^{6,7} reports have characterized products being assessed for therapeutic activity
29	101	against COVID-19. We sought to complement these with a rigorous appraisal of early efforts around
24	102	the world to identify safe and efficacious treatments to address the pandemic. In addition to identifying
	102	investigational therapies, we also characterized the sponsorship, critical design elements and specified
34	104	outcomes of each registered clinical trial. While our analysis represents an early snapshot of a
	105	continually evolving area, it nevertheless provides timely and globally important information for
	106	researchers, policy-makers and the general public.
39	107	researchers, poney makers and the general public.
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40	109	METHODS
	110	Data Sources
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	111	We used information from the World Health Organization's (WHO) clinical trials registry network and
	112	ClinicalTrials.gov. ClinicalTrials.gov is a registry of public and privately funded clinical trials
50	113	conducted around the world maintained by the United States (U.S.) National Library of Medicine on

⁵² 114 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,

⁵⁵₅₆116 Iran, Japan, Lebanon, Thailand, Netherlands, Pan Africa, Peru, Sri Lanka and the United Kingdom.

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2 117 Each participating country sends their data to the International Clinical Trials Registry Platform

(ICTRP) maintained by the WHO.⁸ Both the WHO registry⁹ and ClinicalTrials.gov¹⁰ require that 118

registered trials meet specific criteria for content, quality and validity, accessibility, unique 119

120 identification, technical capacity and administration, and requirements of the International Committee 121 of Medical Journal Editors.

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12 123 **Registry Searches**

14 124 We downloaded all COVID-19 trials provided by the WHO in a Microsoft Excel spread sheet.¹¹ The 15 16 125 WHO curated all COVID-19 trials published on the ICTRP database in an excel file. Therefore, no 17 18¹⁷126 search strategy was applied to the ICTRP database. We also performed a manual search of each of the ¹⁹ 127 WHO's seventeen network registries, such as EU Clinical trials register to identify additional trials, 20 21 128 yielding 21 additional studies. We combined these data with information from the ClincialTrials.gov 22 23 129 registry.¹² All searches were last updated on March 26, 2020. To identify trials registered in the U.S., ²⁴ 130 we searched the ClinicalTrials.gov registry for trials related to the 2019 novel coronavirus using 26 131 keywords "Coronavirus" or "COVID-19" or "COVID19" or "2019 novel coronavirus" or "2019-27 nCoV" or "SARS-CoV-2" (eTable 1). In order to assess whether there were omitted trials, we also 28 1 3 2 29 ²₃₀ 133 searched major medical journals, such as Lancet, New England Journal of Medicine and JAMA, and ³¹ 134 32 websites from the World Health Organization, U.S. Centers for Disease Control and Prevention and 33 135 media aggregators. These searches did not reveal any additional trials to be included in the analysis. 34

³⁶ 37 137 For each product that that was approved by regulators, we searched for information from the European ³⁸ 138 39 Medicines Agency (EMA)¹³ and U.S. Food and Drug Administration (FDA)¹⁴ describing mechanisms 40 1 39 of action and approved indications. We searched the pharmaceutical manufacturers' websites and other 41 42 140 online sources for information about drugs that were not approved in the European Union or the United 44 141 States.

Trial Selection 47 143

48 49 144 We included all studies conducted on patients diagnosed with COVID-19. First, we selected ⁵⁰ 145 interventional clinical trials based on the "study type" variable (eFigure 1). This variable contains 51 52 146 values such as interventional trials, observational studies, expanded access, diagnostic test, basic 53 54 147 science, prevention, prognosis, epidemiological research, health services research and screening. 55 56 148 Interventional studies are "studies that prospectively assign human participants or groups of humans to Page 7 of 27

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one or more health-related interventions to evaluate the effects on health outcomes".^{15,16} To be 149 inclusive of all trials on drugs and plasma, we did not limit our inclusion criteria to randomized trials. 150 151 Second, we included studies where drugs or plasma was the primary intervention. Since there was not 152 standardized information about the components of each intervention, two individuals (KM, HM) 153 independently reviewed each interventional study to identify any trials of a drug or plasma. Any 10 11 154 disagreement was resolved by a third reviewer (GCA). Because study focus was on evaluating drugs 12 155 or plasma treatments, we excluded trials of stem cell transplants, devices, diagnostic tests, traditional 13 14 1 56 Chinese medicines/herbal medicine, rehabilitation, dietary supplements and psychological 15 16 157 interventions. We did not limit any studies based on the outcomes they evaluated. We also excluded 17 18¹⁷158 one trial with implausible information regarding its study design (a single-arm randomized controlled ¹⁹ 159 trial). 20

23 161 **Data extraction and management**

²⁴ 162 We extracted the following information from each trial: unique trial number; trial registry source 26 163 (WHO network registry country or the U.S.), registration date, recruitment status (recruiting, not yet 28 164 recruiting, withdrawn or cancelled), recruitment country, phase (0, 1, 2, 3, 4, 1-2, 2-3, not applicable, ²₃₀ 165 missing), anticipated enrolment, lead sponsor, allocation status (randomized, non-randomized), ³¹ 166 32 intervention model (single-arm, parallel, cross-over, factorial, platform trial, sequential), blinding 33 167 (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 35 168 36 37 169 enrolling by invitation were grouped as recruiting. We used the country address of each facility (i.e., a ³⁸ 170 39 site that can potentially enroll participants) to identify recruitment countries. Enrolment number 40 171 reflects the estimated total number of participants to be enrolled or the actual total number of 42 172 participants enrolled.

⁴⁵ 174 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 47 175 48 49 176 sponsorship as follows: (i) the lead sponsor was considered to be a pharmaceutical company if the ⁵⁰ 177 primary sponsor was a pharmaceutical company, or a known funding body like the National Institutes 52 178 of Health (NIH) was neither a primary sponsor or collaborators/secondary sponsor, and at least one 54 179 collaborator was a pharmaceutical company; (ii) the lead sponsor was a known government research ⁵⁵ 180 funding agency if identified as such or at least one collaborator was this funder; (iii) the lead sponsor

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2 181 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 182 183 record in detail and extracted the information. If, after in depth review, study design was still unclear 184 (n=37), we used the following rules to assign intervention model and blinding: (i) trials with a single 185 group were considered as non-randomized and open-label;¹⁷ (ii) trials that reported more than one 11 186 group were considered having a parallel group design; (iii) trials were considered open-label if blinding 187 was not reported and could not be inferred. We grouped parallel, cross-over, factorial, platform, and 14 188 sequential intervention trials as multi-arm (>2 trial arms).

18¹190 Two reviewers (HM, TM) independently reviewed primary outcomes of all trials and assigned them as ¹⁹ 191 surrogate or biomarker, clinical scale, or clinical outcomes. Surrogate or biomarker included any 21 192 measure of SARS-Cov-2 or any blood test; clinical scales included measures of oxygenation, 23 193 Sequential Organ Failure Assessment (SOFA) score, National Early Warning Score 2 (NEWS2) score, ²⁴ 194 lung injury score or any measure of pulmonary harms; and clinical outcomes included symptoms, 26 195 clinical improvement scores, intubation, hospitalization or death. Reviewer disagreement was resolved 28 196 by discussion and consensus.

³¹ 198 We identified drugs under investigation for COVID-19 from the experimental and/or control arm of 33 199 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 35 200 ³⁶ 37 201 extracted this information, converting brand names were scientific names and correcting minor spelling ³⁸ 202 errors. We used the WHO's Anatomical Therapeutic Chemical Classification System to classify drugs 40 203 in major therapeutic or pharmacological subgroups. For the 18 drugs (e.g., remdesivir) that were not 42 204 included in the WHO's ATC algorithms, we used product information from the European Medicines 43 44 205 Agency, U.S. FDA or the companies' websites to characterize the product.

47 207 Analysis

48 49 208 We used descriptive statistics to analyze the extracted data. We summarized the characteristics of all ⁵⁰ 209 included trials using frequency and percentages. We listed unique drugs under investigation and the 51 52 210 number of registered clinical trials for each product. We plotted the number of cumulative trials by 53 54 211 their registration date. All data was extracted and stored in an open-access Google Sheet document

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² 212 (Link). The study was considered non-human subject research by the Johns Hopkins University

213 Institutional Review Board. We used SAS version 9.4 (SAS Institute Inc.) for all analyses.

⁵₆ 214 **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.

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¹⁷₁₈ 221 **RESULTS**

¹⁹₂₀ 222 Characteristics of Clinical Trials

21 223 Overall 201 clinical trials were registered for testing the therapeutic benefits of 156 drugs or plasma, 22 23 224 including 62 in monotherapy and 92 different combinations (Table 1). Although the trials were ²⁴ 225 initiated in more than 17 countries or regions, 100 (49.8%) were registered in China, and 78 (37.8%) in 26 226 the U.S. Of the 201 trials, 4 (2.0%) were registered in January 2020, 97 (48.2%) in February and 100 27 (49.8%) between March 1st and March 26, 2020 (Figure 1). Nearly 60% of the trials were recruiting 28 2 27 ²⁹ 30 228 patients, and more than half were sponsored by hospitals or universities (55.2%), while about one in ³¹ 229 five were sponsored by a government (19.4%) and a similar proportion (17.9%) were industry 33 2 3 0 sponsored. 34

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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 singleblinding.

46 47 238 **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

243 (42.3%) of trials, primarily assays of viral load. None of the trials assessed patient and public 244 involvement or quality of life as outcome measures.

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246 **Study Size**

247 Overall, the studies projected enrolling a median (IOR) of 100 (IOR, 50-240) patients. Notably 54

11 248 (26.9%) of trials sought to enroll 50 or fewer patients. At the other extreme, 94 (46.8%) trials sought to

¹² 249 enroll 100 or more patients, with 20 (9.6%) studies anticipating enrollment of 500 or more patients.

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16 251 **Therapies Under Evaluation**

17 18 252 Overall 92 drugs or plasma were under investigation, including 64 in monotherapy and 28 different ¹⁹ 253 combinations (Table 2). Only 8 (5.1%) products or combinations involved new molecular entities. The 20 21 254 other test therapies had a wide range of prior medical uses; 412 (18.8%) were antivirals, 9 (14.1%) 22 23 255 immunosuppressants other than corticosteroids, 4 anticancer drugs (6.3%) 3 (4.7%) antimalarials, 2 ²⁴ 256 (3.1%) corticosteroids, 2 (3.1%) immunostimulants and 2 (3.1%) antithrombotic agents. The 28 26 257 different combinations including antivirals, antimalarials, immunosuppressants, immunostimulants and 27 28 2 58 antibacterials (**Table 3**). Of these, nine (32%) were antimalarial/antiviral combinations, seven (25%) ²⁹ 30 259 antiviral/immunosuppressant combination and six (21%) antiviral/interferon combination.

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33 261 34 35 262 DISCUSSION

³⁶ 37 263 This study characterized the scope, objectives, and content of the current global research program to ³⁸ 264 find effective therapies for COVID-19 as reported to the leading clinical trial registries. These data 40 265 show that the primary focus of clinical trial research at present is assess whether a wide range of 42 266 existing therapeutic products might also be effective against acute illnesses caused by the novel SARS-43 44 267 Cov-2 virus. Because one-third of trials exclude clinical endpoints, nearly one half are designed to ⁴⁵ 268 enroll fewer than 100 patients and two-thirds are open label, many of these studies are likely to yield 47 269 only preliminary evidence of a given treatment's safety and effectiveness against COVID-19. 48 49 270

⁵⁰ 271 Our results indicate that current scientific activity is concentrated in China and the United States, 52 272 accounting for 87.6% of the studies. Some of the products under investigation, such as remdesivir, have 54 273 considerable pre-clinical and clinical evidence to support their potential value. In addition to single site ⁵⁵ 274 trials, several major, multi-site trials of therapies against COVID-19 are also underway. Solidarity,

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2 275 announced by the World Health Organization on March 20, 2020, is a multi-center, adaptive, 3 276 randomized, open-label, five arm trial testing remdesivir, chloroquine/hydroxychloroquine, 4 5 277 ritonavir/lopinavir and ritonavir/lopinavir with interferon-beta against standard of care in dozens of 6 7 278 countries around the globe.¹⁸ Discovery, coordinated by France's National Institute of Health and 8 279 Medical Research (Inserm), is designed as an add-on trial in Europe and will study the same drugs with 9 10 11 280 the exclusion of chloroquine.¹⁹ The vast majority of test therapies have been approved for other uses, ¹² 281 although 8 new molecular entities are being assessed, a number that is likely to grow as governments 13 14 282 and industry invest in new compounds during the coming months. 15 16 283 $^{17}_{18}284$ Our findings provide reason for both optimism and caution. Many registered COVID-19 trials have

¹⁹ 285 been designed expediently, and while case series and single-arm trials have value and may provide 20 21 286 early signals, randomized study designs provide higher quality evidence and will maximize chances for 22 23 287 finding effective and safe treatments during this wave of the pandemic. These trial designs, however, ²⁴ 288 need adequate funding as well as scientific leadership, especially as frontline clinicians are tasked with 26 289 saving lives. In addition, it is important that surrogate outcomes, biomarkers or clinical scales are 27 28 290 strongly and directly linked to what matters most for providers and patients, improved chances of 29 30 291 recovery from COVID-19.20,21

33 293 This study provides early evidence of the benefits of global registries to characterize urgent clinical 34 35 294 trial research questions now under investigation. Used wisely by active researchers, these registries can ³⁶ 37 295 help to identify the most promising avenues for developing new therapies, avoid unnecessary ³⁸ 296 duplication, and define unanswered questions that inevitably arise from early research. The registries 39 40 297 also constitute a focal point for developing a more comprehensive program to share protocols and 41 42 298 research results. Given the early use of pre-prints prior to peer review and multiple journals publishing ⁴³ 299 results, the global research enterprise needs to enlarge and extend the cooperative effort initiated by 44 45 300 these registries. 46

⁴⁸₄₉ 302 Limitations

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⁵⁰ 303 Our analysis was limited to a cross-sectional review of trials registered early in the pandemic with one ⁵² 304 half the studies registered in the previous month. Many of these studies appeared to be exploratory and ⁵³ not explicitly powered to test a specific drug effect on a pre-specified primary endpoint. In addition, ⁵⁵ 306 our assessment was limited to drugs and plasma, rather than other treatment modalities under

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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 11 312 analysis is only as good as the data that it is based on; the International Clinical Trials Registry ¹² 313 Platform (ICTRP) gathers information from more than a dozen contributing countries and despite its 14 3 1 4 value, there remain opportunities to improve the consistency and quality of submitted data from both 16 3 1 5 this platform²² and ClinicalTrials.gov.²³ 18 316

21 318 CONCLUSIONS

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23 319 The global pandemic has galvanized the world's research community, and there are signs of ²⁴ 320 remarkable scientific activity.²⁴ In this review of clinical trials registered early in course of the 26 321 pandemic's first wave, we found evidence of rapid clinical investigation of existing antivirals, 28 3 2 2 antimalarials, immunosuppressants and oncology treatments for repurposing against COVID-19. ²⁹ 30 323 Despite this, many registered trials lack features to optimize their scientific value. Global coordination ³¹ 324 and increased funding of high-quality research may help to maximize scientific progress in rapidly discovering safe and effective treatments. 33 325

Clinical Trial Characteristics	Total trials ($N = 201$)
rial intervention, n (%)	· · · · · · · · · · · · · · · · · · ·
Drug	188 (93.5)
Plasma	13 (6.5)
rial 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 (%)	2 (1.0)
Recruiting	120 (59.7)
Not yet recruiting	75 (37.3)
Withdrawn	6 (3.0)
Recruitment country, ^a n (%)	0 (5.0)
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 (%)	27 (19.4)
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 (%)	111 (22.0)
Hospitals	111 (55.2)
Industry	36 (17.9)
Government	39 (19.4)
Other ^b	7 (3.5)
Not reported	8 (4.0)
Percentages may exceed 100% as cate Includes foundations and disease trial SRCTN International Standard Rando Sources: World Health Organization ar	networks

1 trials).

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	Anticipated enrolment, n (%)		
5 6	Median (IQR)	100 (50-240)	
0 7	≤50	54 (26.9)	
8	51-100	53 (26.4)	
9	≥100	94 (46.8)	
10	Outcome, ^a n (%)	<u>_</u>	
11 12	Surrogate/biomarker	85 (42.3)	
12	Clinical scale	33 (16.4)	
14	Clinical outcome	134 (66.7)	
14 15 331 16 332 17 333 18 334 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45			
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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	Malaria, extraintestinal amebiasis, lupu
		DNA; possible antiviral effect on SARS-CoV	erythematosus, rheumatoid Arthritis
		through changing the glycosylation of ACE2	
		receptor and spike protein	
Dihydroartemisinin/piperaquine	1	Blocks a step in P. falciparum parasite's	Malaria
	<u> </u>	metabolism needed for its survival	
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 inhibits hepatitis virus C NS3/4A	Investigational drug for Hepatitis C
Danoprevir/ritonavir	4	protease inhibitor;	
		Darunavir inhibits HIV-1 protease enzyme, thus	HIV-1
Darunavir/cobicistat	1	slowing down multiplication of HIV	
		Inhibits RNA polymerase and prevents	Influenza (Japan)
Favipiravir	11	replication of the viral genome	
		Lopinavir inhibits HIV-1 protease enzyme, thus	HIV-1
Lopinavir/ritonavir	16	slowing down multiplication of HIV	
		Nucleoside analogue; inhibit the action of RNA	None; investigational medicine
Remdesivir	10	polymerase; tested for Ebola, MERS, SARS	
Ribavirin	1	Inhibition of viral RNA and protein synthesis	Hepatitis C
		Inhibitor of influenza virus neuraminidase	Influenza
Oseltamivir	2	affecting release of viral particles	
Umifenovir	6	Inhibits membrane fusion in influenza virus	Influenza (Russia and China)
		Sofosbuvir inhibits HCV NS5B RNA; ledipasvir	Hepatitis C
Sofosbuvir/ledipasvir	1	inhibits HCV NS5A inhibitor	-
Different antiviral combinations ^c	7		
Immunosuppressants	27		
		Blocks tumor necrosis factor – α , thereby	Rheumatoid arthritis, psoriatic arthritis
		reducing inflammation and other symptoms of	Juvenile idiopathic arthritis, Crohn's
		the disease	disease, axial spondyloarthritis, Plaque
Adalimumab	1		psoriasis
Baricitinib	2	Janus kinase inhibitor	Rheumatoid arthritis
Fingolimod	1	Sphingosine 1-phosphate receptor modulator	Multiple sclerosis
	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
		Not fully known; it has immunomodulatory,	Multiple myeloma, erythema nodosum
Thalidomide	2	antiinflammatory and antiangiogenic properties	leprosum
		Interleukin-6 receptor antagonist	Rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, cytokine
Tocilizumab	11		release syndrome
Immunostimulants	16		
Interferon	15	Recombinant cytokine with antiviral properties	Hepatitis B, hepatitis C, leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, malignant melanoma
		Human granulocyte-macrophage colony-	Acute myeloid leukemia, transplantation
Sargramostim	1	stimulating factor	
Anticancer drugs	7		
8		Vascular endothelial growth factor-specific	Several types of cancer; for example,
Bevacizumab	2	angiogenesis inhibitor	colon, lung, breast
Colchicine	2	Tubulin disruption	Gout flare, familial Mediterranean fever
Programmed death receptor-1 (PD-1)		Binds to PD-1 found on T cells, thereby	Several types of cancer, for example,
antagonists	2	inhibiting T cell proliferation	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
Methylpredhisolone	5		Several autoimmune, infectious, and
Immunoglobulins	3		idiopathic diseases
Antithrombotic agents	3		
Heparin	2	—— Inactivation of Factor Xa and Factor IIa	Deep vein thrombosis, pulmonary
Enoxaparin	1		embolism
Antifibrinolytics (Proteinase inhibitors)	2		
Camostat	1	Serine protease inhibitor	Chronic pancreatitis, postoperative reflu esophagitis (Japan)
Ulinastat	1	Urinary trypsin inhibitor	Acute pancreatitis, shock (Japan)
Expectorants (Mucolytics)	2		redice pulleredities, sheek (supul)
	_	Mucolytic agent	Abnormal, viscid, or inspissated mucous
Acetylcysteine	1		secretions
Bromhexine	1	Mucolytic agent	Congestion and cough
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1 1 2 1 1 2 1 1 2 1 2 1 2	Analogue of vasoactive intestinal polypeptideInhibits bacterial protein synthesisInhibit protein synthesis by binding to ribosomesof the bacteriaMonoclonal antibody; PD-1 inhibitorRecombinant fusion protein that targets a novelimmune pathway checkpointSelective alpha2-adrenergic agonistInhibition of an inflammatory response atcellular levelNucleoside analoguesJanus kinase inhibitor	Acute lung injury, sarcoidosis (Europe) Mild to moderate infections Tuberculosis Refractory classical Hodgkin lymphoma (China) Investigational drug Sedation Decongestant, reduction of swelling following injuries Not found
1 1 1 2 1 1	Inhibit protein synthesis by binding to ribosomes of the bacteria Monoclonal antibody; PD-1 inhibitor Recombinant fusion protein that targets a novel immune pathway checkpoint Selective alpha2-adrenergic agonist Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	Tuberculosis Refractory classical Hodgkin lymphom (China) Investigational drug Sedation Decongestant, reduction of swelling following injuries Not found
1 1 1 2 1 1	of the bacteria Monoclonal antibody; PD-1 inhibitor Recombinant fusion protein that targets a novel immune pathway checkpoint Selective alpha2-adrenergic agonist Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	Refractory classical Hodgkin lymphom (China) Investigational drug Sedation Decongestant, reduction of swelling following injuries Not found
1 1 1 2 1 1	Monoclonal antibody; PD-1 inhibitorRecombinant fusion protein that targets a novel immune pathway checkpointSelective alpha2-adrenergic agonistInhibition of an inflammatory response at cellular levelNucleoside analoguesJanus kinase inhibitor	(China) Investigational drug Sedation Decongestant, reduction of swelling following injuries Not found
1	Recombinant fusion protein that targets a novel immune pathway checkpoint Selective alpha2-adrenergic agonist Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	(China) Investigational drug Sedation Decongestant, reduction of swelling following injuries Not found
1	immune pathway checkpoint Selective alpha2-adrenergic agonist Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	Investigational drug Sedation Decongestant, reduction of swelling following injuries Not found
1	immune pathway checkpoint Selective alpha2-adrenergic agonist Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	Sedation Decongestant, reduction of swelling following injuries Not found
1	Selective alpha2-adrenergic agonist Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	Decongestant, reduction of swelling following injuries Not found
1	Inhibition of an inflammatory response at cellular level Nucleoside analogues Janus kinase inhibitor	Decongestant, reduction of swelling following injuries Not found
1	cellular level Nucleoside analogues Janus kinase inhibitor	following injuries Not found
1	Nucleoside analogues Janus kinase inhibitor	Not found
1 1 2	Janus kinase inhibitor	
1		
2		Investigational drug (China)
	Angiotensin II receptor blockers	Hypertension
	Decreases hepatic production and intestinal	Diabetes Mellitus
	absorption of glucose, improves insulin	
1	sensitivity	
1		Investigational drug
5		Hypoxic respiratory failure in neonates
1		Cough suppressant
2		Investigational drug
		Possible anticancer activity
1		
	Renin-angiotensin system peptidase	Possible heart failure therapy
<u> </u>		
1		Melanoma and renal cell carcinoma
	Mediating I cell tolerance	Neutrophil-mediated inflammatory
<u> </u>		disease
1		Erectile dysfunction
1	Macrofilaricidal	African sleeping sickness and river
<u> </u>	5 D 1 (1 1	blindness (Africa)
5		Investigational drug for cancer
		bronchial asthma, keloid, hypertrophic
1	mmonor	scar, and allergic disorders (Japan and South Korea)
1	Guanina nucleatide analogue that inhibits DNA	Influenza A and B infections (Russia)
1	6	influenza A anu D inflections (Kussia)
1	synthesis	
	1 5 1 2 1 1 1 1 1 1 1 1 1 1 2 1 1 2 1 2	1 Opium alkaloid 2 Agonists of Toll-like receptors Upregulation of antitumor genes and the 1 induction of cell apoptosis Renin-angiotensin system peptidase 1 T cell growth factor Mediating T cell tolerance 1 Sigma receptor agonist activity Macrofilaricidal 1 5-Da polypeptide hormone Hematopoietic prostaglandin D synthase inhibitor 1 Guanine nucleotide analogue that inhibits RNA 1

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

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	Registered trials,
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
Antivitais + Interferon Asc09/ritonavir + interferon	1
Favipiravir + interferon	1
Lopinavir/ritonavir + interferon	6
Ribavirin + interferon	2
Ribavirin + lopinavir/ritonavir + interferon	
Umifenovir + interferon	$\frac{1}{2}$
Other combinations	3
Darunavir/cobicistat + thymosin	1
Lopinavir/ritonavir + thymosin	1
Ebastine + interferon + lopinavir	1

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

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.

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C. Funding

None

D. Data Sharing Statement

Data is stored in an open-access Google Sheet document https://docs.google.com/spreadsheets/d/1p_229olyi7ft6MCLYXdS4dkKszjnAiSnLRVO68OLk8/edit#gid=0

E. Acknowledgements

The authors gratefully acknowledge Kristin Meek, Matthew Tajanlangit and Jamie Heyward for assistance extracting information from trial registries and Sneha Sura for assistance reviewing drug information and data management.

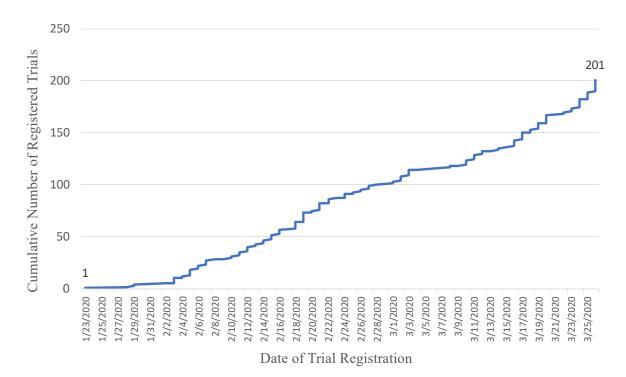
ht	World Health Organization Dashboard. Available at: <u>ps://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd</u> (Accessed Apr. 20).
Sc	Coronavirus Resource Center. Coronavirus COVID-19 Global Cases by the Center for System ience and Engineering. Available at: <u>https://coronavirus.jhu.edu/data/new-cases</u> (Accessed A 20).
27	Harrison C. Coronavirus puts drug repurposing on the fast track. Nature Biotechnology. Feb , 2020. Available at: <u>https://www.nature.com/articles/d41587-020-00003-1</u> (Accessed April 20).
	Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With onvalescent Plasma. JAMA. Published online March 27, 2020. doi:10.1001/jama.2020.4783
22	Zimmer C. Scientists Identify 69 Drugs To Test Against the Coronavirus. New York Times. N., 2020. Available at: <u>https://www.nytimes.com/2020/03/22/science/coronavirus-drugs-loroquine.html</u> (Accessed March 25, 2020).
<u>ht</u>	The Milken Institute. COVID-19 Treatment and Vaccine Tracker. Available at: <u>ps://milkeninstitute.org/sites/default/files/2020-03/Covid19-Tracker-3-36-20-FINAL.pdf</u> (Acal arch 25, 2020).
A	Garde D. An Updated Guide to the Coronavirus Drugs and Vaccines in Development. STAT Mailable at: <u>https://www.statnews.com/2020/03/19/an-updated-guide-to-the-coronavirus-drugs</u> ccines-in-development/ (Accessed March 26, 2020).
	nternational Clinical Trials Registry Platform (ICTRP). World Health Organization. Availa https://www.who.int/ictrp/network/primary/en/ (Accessed March 26, 2020).
	World Health Organization Data Set. International Clinical Trials Registry Platform (ICTRP). vailable at: <u>https://www.who.int/ictrp/network/trds/en/</u> (Accessed March 25, 2020).
O	ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and oservational Studies. National Library of Medicine. Available at: <u>cps://prsinfo.clinicaltrials.gov/definitions.html</u> (Accessed March 25, 2020).
	World Health Organization Database of COVID-19 Trials. Available at: who.int/ictrp/en/ ccessed March 25, 2020).
	ClinicalTrials.gov. National Library of Medicine. Available at: <u>www.clinicaltrials.gov</u> (Acc arch 25, 2020).
	European Medicines Agency. Available at: <u>https://www.ema.europa.eu/en</u> (Accessed March 20).
14	U.S. Food and Drug Administration. Available at: FDA.gov (Accessed March 25, 2020).
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Observat	alTrials.gov Protocol Registration Data Element Definitions for Interventional and ional Studies. ClinicalTrials.gov. March 7, 2019. Available at: <u>rsinfo.clinicaltrials.gov/definitions.html</u> (Accessed March 25, 2020).
¹⁷ Califf	RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of Clin egistered in ClinicalTrials.gov, 2007-2010. JAMA. 2012;307:1838–1847.
	ealth chief announces global 'solidarity trial' to jumpstart search for COVID-19 treatment s. March 18, 2020. Available at: <u>https://news.un.org/en/story/2020/03/1059722</u> (Accesse 2020).
treatmen	rschmidt K, Cohen J. WHO launches global megatrial of the four most promising corona ts. Science. March 22, 2020. Available at: <u>https://www.sciencemag.org/news/2020/03/w</u> -global-megatrial-four-most-promising-coronavirus-treatments (Accessed April 3, 2020).
	k MJ, Senthil M, Wall NR. Making Meaningful Clinical Use of Biomarkers. Biomark 2017;12:1-7.
	er MJ, Pignone M. Evaluating the clinical utility of a biomarker: a review of methods for ag health impact. Circulation. 2011;123:1116-24.
-	ever RF, Karam G, Reis A, Ghersi D. The quality of registration of clinical trials: still a PLoS One. 2014;9:e84727.
	Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in 10 issues to consider. BMJ. 2018;361:k1452
	o M, Kirkpatrick DD. Covid-19 Changed How the World Does Science, Together. New April 1, 2020. Available at: <u>https://www.nytimes.com/2020/04/01/world/europe/coronavir</u>
Times. A science-r	
Times. A science-r	ed April 1, 2020).
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Figure 1. Cumulative Number of Registered Clinical Trials of Products for SARS-CoV-2 Infection.

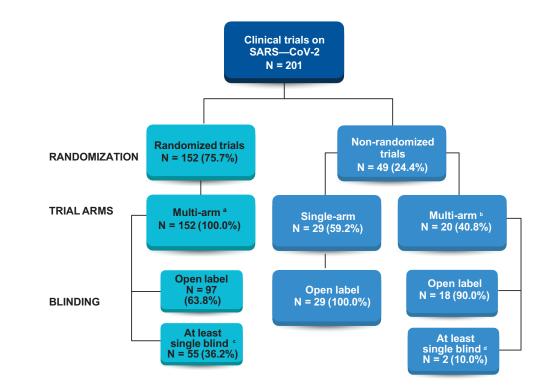


Sources: World Health Organization and ClinicalTrials.gov (as of March 26, 2020)

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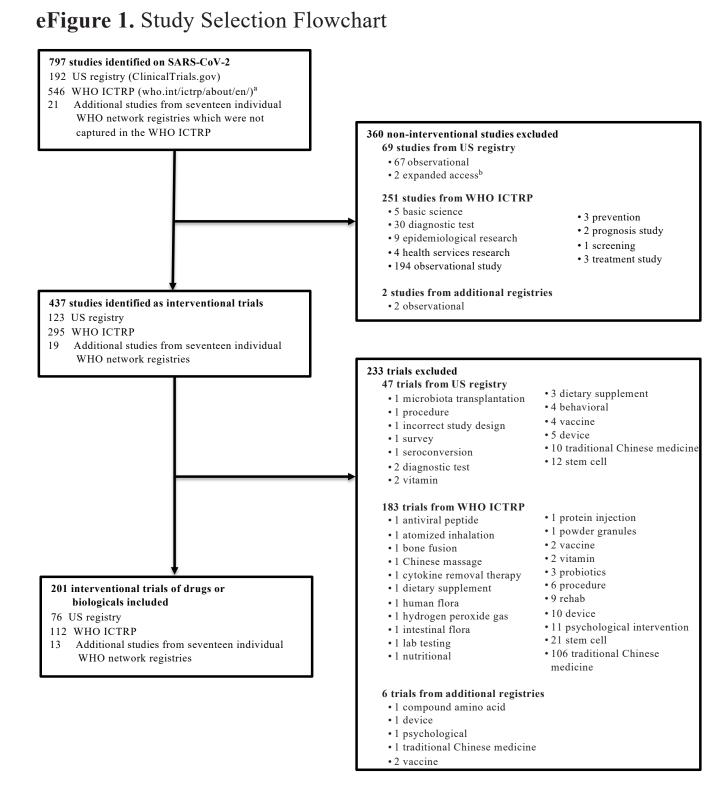
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Figure 2. Study Designs of Registered Clinical Trials of Products for SARS-CoV-2 Infection (N=201 trials).



^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)

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ICTRP International Clinical Trials Registry Platform; WHO World Health Organization

^aTo avoid double counting we excluded 121 studies which were originally registered in the US registry

^bExpanded 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.

	BMJ Open	Pag
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
B 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 metavanalysis. http://bmjopen.bmj.com/site/about/guidelines.xhtml	7

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PRISMA 2009 Checklist

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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).		
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 selection17Give 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	
esults 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	

41 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.
42 doi:10.1371/journal.pmed1000097

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