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Characteristics of COVID-19 Clinical Trials Registered with ClinicalTrials.gov: Cross-Sectional Analysis

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Objectives: To characterize current COVID-19-related research activities

Design: Cross-sectional analysis

Setting: Clinical trials registered with ClinicalTrials.gov testing interventions relevant to COVID-19.

Data Sources: ClinicalTrials.gov was searched for COVID-19 and related terms to identify trials registered between December 1, 2019 and May 1, 2020 that test interventions related to the COVID-19 pandemic.

Main Outcome Measures: We classified trials according to intervention type, and report key trial characteristics including recruitment status, location, funder type, target enrollment number, intervention model (single group, randomized, or sequential assignment), and projected completion date.

Results: Of the 630 identified clinical trials related to COVID-19, 509 (81%) involved the study of drugs or biologic agents. Of these trials of drugs and biologics, 305 (60%) use an open-label design, 43 (8%) are single-blinded (participant only), and 161 (32%) are double-blinded (participant and investigator). 94 (18%) of the drug/biologic trials are non-randomized. Either hydroxychloroquine or chloroquine are administered as part of the study protocol in 152 (30%) of the drug/biologic trials. The total planned enrollment for these hydroxychloroquine/chloroquine trials is over 200,000 participants, which represents 65% of the total planned enrollment for all registered trials of drugs or biologics. There are also at least 25 registered trials of azithromycin (n = 53) convalescent plasma (n = 38), lopinavir/ritonavir (n = 30), stem cell treatments (n = 29), and tocilizumab (n = 25). 142 trials were registered in the first three months of 2020, and 488 trials were registered between April 1 and May 1, 2020.

Conclusions: These findings demonstrate a robust research response to the COVID-19 pandemic, though many of the currently planned and ongoing trials focus on a small number of potential therapies, and many also lack essential design features and power necessary to provide accurate treatment effect estimates.

Strengths and Limitations of this study:

- The study includes data from studies registered at ClinicalTrials.gov, the largest clinical trial registry in the world.
- The comprehensive search strategy used by investigators is likely to have identified most relevant trials within the ClinicalTrials.gov database.
- Registry data are subject to change over time, including estimates of the number of planned trials and the number of expected trial participants.

Characteristics of COVID-19 Clinical Trials Registered with ClinicalTrials.gov: Cross-Sectional Analysis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has generated an unprecedented clinical research response. While this response has tremendous potential to save lives and improve the wellbeing of people across the globe, the magnitude of the response poses risks. In particular, there is a risk that the poor choice of research questions, use of suboptimal study designs, and the failure to coordinate research activities will result in wasted research resources.(1, 2) These at-risk resources include money and supplies, effort on the part of investigators and study personnel, and perhaps most importantly, time. A number of experts have predicted that even after the present COVID-19 outbreak declines, recurrent outbreaks are possible or even likely.(3) It is therefore critical to make efficient use of time in the search for effective treatment and preventative measures.

Optimizing the efficiency of research efforts requires some degree of coordination across the biomedical research community. A prerequisite to the coordination of COVID-19 research effort is the characterization of current research activities. Specifically, a better understanding is needed of the types of trials planned or in progress, the specific treatments to be studied, and the number of patients expected to be included. Collectively, this information has the potential to maximize the clinical utility of ongoing and future research efforts.(4) Specific uses might include determining which interventions need additional research, identifying groups of studies for which harmonization of inclusion criteria, dosing, and outcomes might be beneficial to facilitate pooled analyses, and aiding clinicians and policy makers in the interpretation of positive or negative findings from single studies. The objective of this study is to characterize current COVID-19-related research activities.

METHODS

ClinicalTrials.gov

As of May 2020, ClinicalTrials.gov contained protocol information for over 330,000 studies from 210 different countries, making it by far the largest registry of clinical trials.(5) Information for registered studies is generally entered into ClinicalTrials.gov by study sponsors or investigators, after which it undergoes a quality-control process before study information is made publicly available. Study information can be updated over time, and the registry includes a public audit trail of changes made to previously posted entries. Any human-subject clinical trial that is performed in accordance with local ethical and governmental regulations is eligible for registration with ClinicalTrials.gov.(6) Registration with ClinicalTrials.gov is required for most human-subject trials involving drugs or devices regulated by the US Food and Drug Administration that either are conducted in the United States, are conducted under an investigational new drug application or investigational device exemption, or involve the export of a drug or device manufactured in the US.(7)

Registry Search

We searched ClinicalTrials.gov on May 1, 2020 for trials registered after December 1, 2019 that tested interventions relevant to the COVID-19 pandemic. The search was performed using the following key words in the ClinicalTrials.gov "condition or disease" field: COVID-19 OR COVID OR SARS-CoV-2 OR coronavirus OR corona virus OR 2019-nCoV OR 2019 novel coronavirus OR severe acute respiratory syndrome coronavirus 2. We reviewed the individual registry entries for each of the studies identified by this search, and excluded those that did not meet the definition of a clinical trial adopted by the World Health Organization (WHO): any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.(8) Based on this definition we excluded observational studies, expanded access studies, and simulation or mannequin-based studies. We also excluded studies withdrawn prior to initiating enrollment

and studies not relevant to COVID-19. We classified the remaining trials according to intervention type: drugs/biologics, vaccines, behavioral health or mental health interventions, physiologic interventions (e.g. prone positioning, ventilator settings), medical devices, and other interventions. Trials were included in more than one intervention category when relevant.

Classification of Drug Trials

Those trials testing drugs or biologics were categorized according to the specific agents administered in each study. We grouped trials testing hydroxychloroquine or chloroquine together based on the similar structure and function of these drugs.(9) We considered trials to involve a particular drug or biologic if that specific drug/biologic was administered to participants in any of the trial's treatment arms as a part of the trial protocol. For trials with one treatment arm we considered a drug to be an intervention of interest if it was administered to all of the subjects in that study arm. For trials with multiple treatment arms we considered a drug to be an intervention of interest if the study design facilitated an evaluation of the drug's efficacy by either administering it to participants in some but not all of the study arms, or by administering different doses or methods of administration to participants in different arms. We also distinguished between drug/biologic trials testing interventions for use in the treatment of patients with active COVID-19 disease from those testing interventions in a prophylactic capacity in order to prevent infection with COVID-19.

Data Collection and Reporting

We report key study design characteristics based on the registered information for each included trial. These characteristics include trial location(s), funder type(s), target enrollment number, intervention model (single group, randomized, or sequential assignment), and anticipated primary completion date, which represents the date on which data collection is completed for the trial's primary outcome measure. Trials were classified as unblinded if participants were not masked to their assigned treatment group, single-blind if participants were masked to the group assignment and investigators were not, and double

blind if both participants and investigators were masked to the group assignment. We also describe the subject recruitment status recorded as of May 1, 2020 for each trial. This reflects the recruitment status at the time of initial registration, or as of the most recent update to the registry record for entries that have been updated. Because the recruitment status field may not be updated immediately after the initiation of enrollment, we also report the number of trials for which the registered "Study Start Date" has passed. We also report the primary completion date for the included trials, which reflects the final date on which primary outcome data is generated for the final trial participant. We obtained counts for the total number of individuals worldwide confirmed to have COVID-19 from the WHO.(10)

Data Analysis

We classified the included trials based on the category of intervention tested, and further classified trials of drugs or biologics based on the specific agent under investigation. Descriptive data are presented for each category, including proportions for categorical data and medians with interquartile ranges for continuous data. When relevant the number of registry entries with missing data is reported for each categorical variable. These analyses were performed using SPSS version 26.0 (SPSS Inc, Chicago, IL).

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this work.

RESULTS

Our search of ClinicalTrials.gov resulted in 1189 potentially eligible studies, 630 of which were clinical trials meeting our inclusion criteria (Figure 1). The majority of trials (n = 509, 81%) study drugs or biologic agents (Table 1). Twenty-six trials study physiologic interventions, most of which involve the study of mechanical ventilation strategies or prone positioning. There were 18 registered trials involving

vaccines; seven of these involve testing the effects of tuberculosis or measles vaccines on COVID-19 susceptibility, and 11 test vaccines specifically designed for the SARS-CoV-2 virus.

Among the trials testing drugs or biologic agents, 305 (60%) are designed as open-label studies (Table 2). Eight percent (n = 43) are single-blinded and less than one third (n = 161, 32%) mask both participants and investigators to the group assignment. Random allocation is used in 415 (82%) of the drug/biologic trials; 94 (18%) do not randomize participants.

The drug/biologic trials involve the study of 218 unique agents. The most commonly studied drugs are hydroxychloroquine or chloroquine, which are administered in 152 (30%) of the drug/biologic trials. Eighty-eight of these are treatment trials assessing hydroxychloroquine/chloroquine as a treatment of interest for COVID-19 patients, 38 study the prophylactic use of these drugs, two have both treatment and prophylactic arms, and 24 administer hydroxychloroquine/chloroquine as part of standard treatment to all participants in multi-arm studies. The total planned enrollment for the hydroxychloroquine/chloroquine trials is over 211,000 participants, which represents 65% of the total planned enrollment for all currently registered trials of drugs or biologics.

Azithromycin is administered in 53 trials, 47 (89%) of which also involve the administration of hydroxychloroquine or chloroquine. There are also 25 or more registered trials of convalescent plasma (n = 38), lopinavir/ritonavir (n = 30), stem cell treatments (n = 29), and tocilizumab (n = 25). Among these trials, the proportion with double-blinded designs ranges from 17% (lopinavir/ritonavir) to 34% (stem cell treatments). The proportion of studies utilizing randomized allocation ranges from 50% (convalescent plasma) to 93% (lopinavir/ritonavir).

Based on the most recent update to the ClinicalTrials.gov “Recruitment Status” field for each of the 630 included trials, 314 (50%) had not yet started enrollment, 287 (46%) were currently enrolling participants,

and 16 (3%) had suspended or completed enrollment. As of May 1, 2020, review of each trial's registered "Study Start Date" and "Primary Completion Date," showed 534 trials (85%) that had passed the date on which recruitment was scheduled to begin but had not yet reached the anticipated primary completion date. The registered primary completion date had passed for 56 trials (9%). Analysis of the timing of registration for new interventional trials related to COVID-19 shows that 142 trials were registered in the first three months of 2020, and 488 trials were registered from April 1 to May 1(Figure 2). Discrepancies between data from the recruitment status field and the registered start and completion dates are likely to reflect either delays in updating the recruitment status field after this status has changed, or a change in the trial schedule relative to the schedule anticipated at the time of registration. Ninety-eight trials (16%) are targeting completion by May 31, 2020, 244 (39%) by July 31, and 346 (55%) by September 30. For 173 trials (27%) the planned primary completion date is in 2021 or later.

DISCUSSION

As of May 1 2020, 630 trials had been registered with ClinicalTrials.gov to study interventions related to COVID-19 infection. Together these trials investigate 218 different drugs or biologic agents, though nearly one-third involve the study of hydroxychloroquine or chloroquine. Trials of hydroxychloroquine or chloroquine plan to enroll over 210,000 participants in total, which represents nearly two-thirds of the planned enrollment for all currently registered COVID-19-related trials assessing drugs or biologics. Additionally, azithromycin, convalescent plasma, lopinavir/ritonavir, and stem cells are each being studied in at least 25 trials. Many of these trials lack essential design features such as blinding and randomized allocation of participants that are essential for using results to accurately estimate treatment effect.(11)

The data included in this analysis provide an overview of many of the initial clinical trials launched in response to the COVID-19 pandemic. Several important factors should be considered when interpreting

these findings. First, while ClinicalTrials.gov is the largest trial registry in the world, many trials are either only listed in other registries or not registered at all, and there may be systematic study design differences between those trials registered with ClinicalTrials.gov and those that are not.(12-14) Despite this potential limitation, our dataset reflects a geographically diverse cohort of trials, including a large number of trials enrolling participants in both Europe and Asia. Similarly, while we utilized a comprehensive search strategy to find relevant trials within the ClinicalTrials.gov database, it is possible that this search failed to identify some relevant COVID-19 trials. Furthermore, it is also possible that some of the currently registered trials will never be initiated. Finally, we present data reflecting registry entries for each of the included trials as of May 1, 2020. While some registry data-fields such as the chosen blinding strategy or the method of allocation are unlikely to change over time, others such as the recruitment status routinely change over the course of a trial. In some cases, updates to individual registry entries may be delayed, and the therefore data reflected in the public registry may be out of date.(15) For example, a number of the included trials had a recruitment status indicating that enrollment had not yet started, but the registered enrollment start date had passed. These discrepancies are likely to reflect either delays in updating the recruitment status field, or changes to a trial's enrollment schedule relative to what was anticipated at the time of registration.(16)

Our findings show a rapid increase in the number of trials registered starting in early April, approximately three weeks after the WHO declared COVID-19 a pandemic. These findings also indicate a profound lack of coordination of existing COVID-19 trials, which consequently increases the likelihood of wasted research effort and also poses risks.(17) Even under normal circumstances, clinical research often results in waste due to in part to inadequate power, suboptimal study design, and early termination.(2, 11, 18) Although attempting to confirm previously observed results through the replication of prior studies is important, the simultaneous conduct of numerous trials that test the same intervention is unlikely to be an optimally efficient allocation of research resources.(2) The problem of waste may be further exacerbated during the study of a pandemic disease in which 1) there exists limited relevant foundational research, 2)

fluctuating case volumes make enrollment projections challenging, and 3) knowledge about the disease changes rapidly during the first few months, resulting in changes in regard to what is considered standard treatment.(19) For several of the drugs studied, the conduct of numerous small trials increases the risk for spurious findings which would add to confusion regarding treatment efficacy and might make it difficult for regulatory boards and clinicians to judge if there is clinical equipoise for larger trials.(20) Several of the included studies are directly competing for patients, increasing the risk that enrollment targets will not be met in a timely manner. Finally, performing pooled analyses may be challenging due to differences in inclusion criteria, dosing, and outcomes.(21-23) Centralized coordination of studies, particularly in the form of large-scale platform or adaptive trials, reduces the risk of bias and increases the potential to identify an effective treatment.(24, 25) The NIH ACTIV partnership is one such promising effort to improve trial coordination.(26)

Further follow-up of the included trials through the results dissemination phase will ultimately help to assess the potential impact that these trials may have on clinical decision-making and patient outcomes.(27) Several COVID-19 related trials have already completed enrollment and results have been published.(28, 29) Results from many additional trials will be published over the coming months. Utilization of trial registry data will be critical to the interpretation of these results by helping the medical community assess for the presence of publication bias among this initial group of publications.(30, 31) This will be particularly important given that there are several interventions each being studied in a large number of trials. For example, if all 88 hydroxychloroquine/chloroquine trials defined a statistically significant result based on a two-sided p-value of 0.05, even in the absence of any true drug affect we would expect about 4 of these trials to report a statistically significant treatment effect due to chance alone.(20)

Our findings illustrate the potential for ClinicalTrials.gov and other registries to aid sponsors and investigators in reducing waste by informing design decisions for future COVID-19 trials. Specifically, in

addition to utilizing study design features that help to produce unbiased estimates of treatment effects, key stakeholders should also utilize registry data to prioritize the conduct of trials that address important but relatively under-studied clinical questions. Future assessment of COVID-19 trials including monitoring of enrollment rates, determining characteristics associated with early termination versus successful trial completion, and evaluating timely outcome reporting will help to inform policies aimed at increasing the value of trials for this and subsequent pandemic events.

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Ethics Approval: Not required

Transparency: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

REFERENCES

1. Altman DG. The scandal of poor medical research. *BMJ*. 1994;308(6924):283-4.

2. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet*. 2014;383(9912):166-75.

3. Chavez C, Another wave of coronavirus will likely hit the US in the fall. Here's why and what we can do to stop it. CNN, May 2, 2020; https://www.cnn.com/2020/05/02/health/coronavirus-second-wave-fall-season/index.html.

4. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020 Apr 13. doi: 10.1001/jama.2020.6019.

5. Clinicaltrials.gov: Trends, Charts, and Maps: U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/resources/trends. Accessed May 11, 2020.

6. Clinicaltrials.gov: Submit Studies: U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/manage-recs. Accessed May 11, 2020.

7. Department of Health and Human Services. Clinical Trials Registration and Results Information Submission. Fed Regist. 2016; 81(183).

8. International Clinical Trials Registry Platform (ICTRP): World Health Organization. https://www.who.int/ictrp/en/. Accessed May 11, 2020.

9. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. *BMJ*. 2020;369:m1432.

10. WHO Coronavirus Disease (COVID-19) Dashboard: World Health Organization; 2020. Available from: https://covid19.who.int/. Accessed May 9, 2020.

11. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med*. 2012;157(6):429-38.

12. Hunter KE, Seidler AL, Askie LM. Prospective registration trends, reasons for retrospective registration and mechanisms to increase prospective registration compliance: descriptive analysis and survey. *BMJ Open*. 2018;8(3):e019983.

13. Loder E, Loder S, Cook S. Characteristics and publication fate of unregistered and retrospectively registered clinical trials submitted to The BMJ over 4 years. *BMJ Open*. 2018;8(2):e020037.

14. Tan AC, Jiang I, Askie L, Hunter K, Simes RJ, Seidler AL. Prevalence of trial registration varies by study characteristics and risk of bias. *J Clin Epidemiol.* 2019;113:64-74.

15. Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. *BMJ*. 2018;361:k1452.

16. Jones CW, Safferman MR, Adams AC, Platts-Mills TF. Discrepancies between ClinicalTrials.gov recruitment status and actual trial status: a cross-sectional analysis. *BMJ Open.* 2017;7(10):e017719.

17. Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. *Lancet*. 2014;383(9912):156-65.

18. Ioannidis JP. Clinical trials: what a waste. *BMJ*. 2014;349:g7089.

19. Klitzman R. Evolving Challenges and Research-Needs Concerning Ebola. *Am J Public Health*. 2015;105(8):1513-5.

20. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. 2017;46(2):746-55.

21. Bangdiwala SI, Bhargava A, O'Connor DP, et al. Statistical methodologies to pool across multiple intervention studies. *Transl Behav Med*. 2016;6(2):228-35.

22. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J*. 2014;35(47):3336-45.

23. Halpern SD, Karlawish JH, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA*. 2002;288(3):358-62.

24. Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov*. 2019;18(10):797-807.

25. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*. 2015;313(16):1619-20.

26. NIH to launch public-private partnership to speed COVID-19 vaccine and treatment options: National Institutes of Health. https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options. Accessed April 26, 2020.

27. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet*. 2014;383(9913):267-76.

28. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 2020;3(4):e208857.

29. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382(19):1787-99.

30. Song SY, Koo DH, Jung SY, Kang W, Kim EY. The significance of the trial outcome was associated with publication rate and time to publication. *J Clin Epidemiol.* 2017;84:78-84.

31. DeVito NJ, Goldacre B. Catalogue of bias: publication bias. *BMJ Evid Based Med*. 2019;24(2):53-4.

Table 1: Characteristics of COVID-19 related clinical trials registered with ClinicalTrials.gov from December 1, 2019 to April 19, 2020.

Trial Characteristics	All Trials (n = 630)
Enrollment Status, No. (%)	
Not yet recruiting	314 (50)
Recruiting	287 (46)
Active, not recruiting	13 (2)
Enrollment completed	11 (2)
Stopped early/suspended	5 (1)
Intervention, No. (%)[a]	
Drug/biologic	509 (81)
Behavioral/mental health	28 (4)
Physiologic	26 (4)
Device	28 (4)
Vaccine[b]	18 (3)
Other	27 (4)
Funding Source, No. (%)[a]	
Industry	143 (23)
NIH[c]/US government	11 (2)
Other/none	558 (89)
Location[a]	
Europe	215 (34)
United States	192 (30)
China	74 (12)
Other Asia	56 (9)
Other	89 (14)
Not specified	24 (4)
Number of participants, median (IQR)	150 (60-401)

[a] Trials may be listed in more than one category; totals therefore add to more than 100%.
[b] Includes seven vaccine trials that study the effect of tuberculosis or measles vaccines on the incidence of COVID-19 infection rather than a vaccine specific to the novel coronavirus.
[c] National Institutes of Health

Table 2: Characteristics of registered COVID-19 trials assessing drugs or biologic agents.

Trial Characteristics	All Drugs/ Biologics (n = 509)	HCQ Treatment[a,b] (n = 90)	HCQ Prophylaxis[a] (n = 40)	Convalescent Plasma (n = 38)	Lopinavir/ Ritonavir (n = 30)	Stem Cells (n = 29)
Trial phase, n (%)[c]						
Phase I	34 (7)	5 (6)	1 (3)	6 (16)	0	8 (28)
Phase II	202 (40)	25 (28)	10 (25)	17 (45)	7 (23)	17 (59)
Phase III	183 (36)	46 (51)	24 (60)	7 (18)	13 (43)	3 (10)
Phase IV	43 (8)	11 (12)	1 (3)	0	6 (20)	0
Other/Not specified	47 (9)	3 (3)	4 (10)	8 (21)	4 (13)	1 (3)
Allocation method, n (%)						
Randomized	415 (82)	79 (88)	36 (90)	19 (50)	28 (93)	19 (66)
Non-randomized	94 (18)	11 (12)	4 (10)	19 (50)	2 (7)	10 (34)
Number of trial arms, n (%)						
Single	74 (15)	10 (11)	2 (5)	17 (45)	0	8 (28)
Multiple	435 (85)	80 (89)	38 (95)	21 (55)	30 (100)	21 (72)
Blinding, n (%)						
Open label	305 (60)	58 (64)	12 (30)	28 (74)	23 (77)	17 (59)
Single (participant)	43 (8)	10 (11)	5 (13)	2 (5)	2 (7)	2 (7)
Double (participant and investigator)	161 (32)	22 (24)	23 (58)	8 (21)	5 (17)	10 (34)
Prophylaxis trial, n (%)	57 (11)	2 (2)[d]	40 (100)	1 (3)	3 (10)	2 (7)
Number of participants, median (IQR)	150 (60-413)	400 (148-655)	825 (374-1729)	85 (20-235)	250 (80-550)	30 (20-78)

[a] Includes trials of hydroxychloroquine or chloroquine.
[b] Azithromycin trials (n = 53) not listed as 47 of these also involve hydroxychloroquine or chloroquine.
[c] Phase I/II trials classified as phase II, phase II/III trials classified as phase III.
[d] Two hydroxychloroquine trials included both treatment and prophylaxis arms.

Figure 1. Flowchart of included trials.

Figure 2: Timeline describing the registration and conduct of COVID-19 clinical trials along with the global total of confirmed COVID-19 cases.

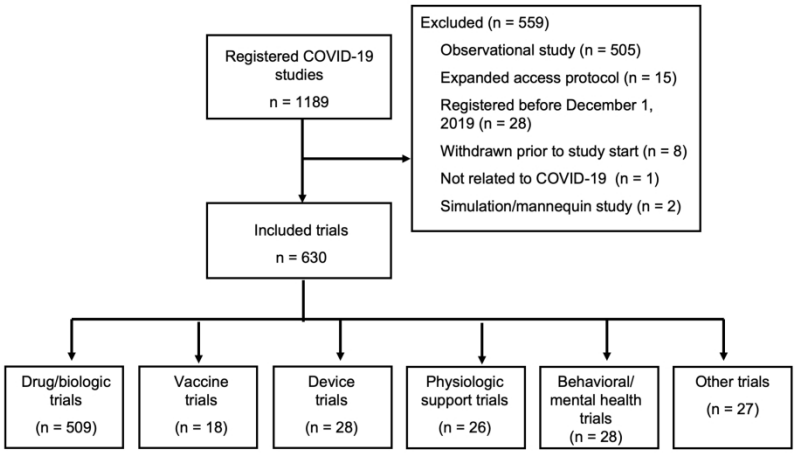

Figure 1. Flowchart of included trials.

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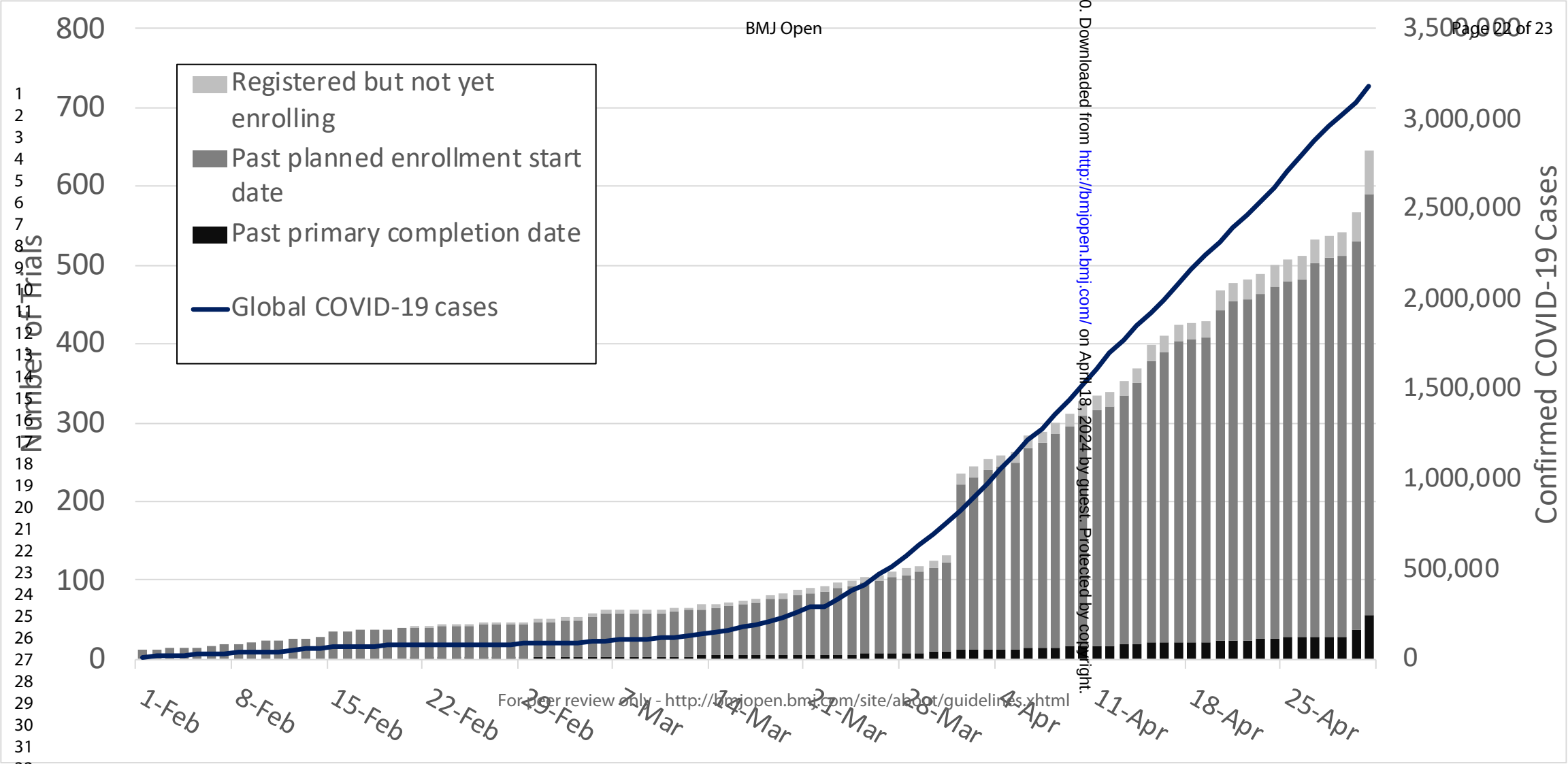

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1,2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	None

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Characteristics of COVID-19 Clinical Trials Registered with ClinicalTrials.gov: Cross-Sectional Analysis

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Characteristics of COVID-19 Clinical Trials Registered with ClinicalTrials.gov: Cross-Sectional Analysis

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Word Count: 3257

Objectives: To characterize current COVID-19-related research activities

Design: Cross-sectional analysis

Setting: Clinical trials registered with ClinicalTrials.gov testing interventions relevant to COVID-19.

Data Sources: ClinicalTrials.gov was searched for COVID-19 and related terms to identify trials registered between December 1, 2019 and May 1, 2020 that test interventions related to the COVID-19 pandemic.

Main Outcome Measures: We classified trials according to intervention type, and report key trial characteristics including recruitment status, location, funder type, target enrollment number, intervention model (single group, randomized, or sequential assignment), and projected completion date.

Results: Of the 630 identified clinical trials related to COVID-19, 509 (81%) involved the study of drugs or biologic agents. Of these trials of drugs and biologics, 305 (60%) use an open-label design, 43 (8%) are single-blinded (participant only), and 161 (32%) are double-blinded (participant and investigator). 94 (18%) of the drug/biologic trials are non-randomized. Either hydroxychloroquine or chloroquine are administered as part of the study protocol in 152 (30%) of the drug/biologic trials. The total planned enrollment for these hydroxychloroquine/chloroquine trials is over 200,000 participants, which represents 65% of the total planned enrollment for all registered trials of drugs or biologics. There are also at least 25 registered trials of azithromycin (n = 53) convalescent plasma (n = 38), lopinavir/ritonavir (n = 30), stem cell treatments (n = 29), and tocilizumab (n = 25). 142 trials were registered in the first three months of 2020, and 488 trials were registered between April 1 and May 1, 2020.

Conclusions: These findings demonstrate a robust research response to the COVID-19 pandemic, though many of the currently planned and ongoing trials focus on a small number of potential therapies, and many also lack essential design features and power necessary to provide accurate treatment effect estimates.

Strengths and Limitations of this study:

- The study includes data from studies registered at ClinicalTrials.gov, the largest clinical trial registry in the world.
- The comprehensive search strategy used by investigators is likely to have identified most relevant trials within the ClinicalTrials.gov database.
- Registry data are subject to change over time, including estimates of the number of planned trials and the number of expected trial participants.

Characteristics of COVID-19 Clinical Trials Registered with ClinicalTrials.gov: Cross-Sectional Analysis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has generated an unprecedented clinical research response. While this response has tremendous potential to save lives and improve the wellbeing of people across the globe, the magnitude of the response poses risks. In particular, there is a risk that the poor choice of research questions, use of suboptimal study designs, and the failure to coordinate research activities will result in wasted research resources.(1, 2) These at-risk resources include money and supplies of drugs, effort on the part of investigators and study personnel, and perhaps most importantly, time. A number of experts have predicted that even after the present COVID-19 outbreak declines, recurrent outbreaks are possible or even likely.(3) It is therefore critical to make efficient use of time in the search for effective treatment and preventative measures.

Optimizing the efficiency of research efforts requires some degree of coordination across the biomedical research community. A prerequisite to the coordination of COVID-19 research effort is the characterization of current research activities. Specifically, a better understanding is needed of the types of trials planned or in progress, the specific treatments to be studied, and the number of patients expected to be included. Collectively, this information has the potential to maximize the clinical utility of ongoing and future research efforts.(4) Specific uses might include determining which interventions need additional research, identifying groups of studies for which harmonization of inclusion criteria, dosing, and outcomes might be beneficial to facilitate pooled analyses, and aiding clinicians and policy makers in the interpretation of positive or negative findings from single studies. The objective of this study is to characterize current COVID-19-related research activities with respect to the interventions under

investigation and the design features of registered trials in order to identify opportunities to reduce wasted resource utilization.

METHODS

ClinicalTrials.gov

As of May 2020, ClinicalTrials.gov contained protocol information for over 330,000 studies from 210 different countries, making it by far the largest registry of clinical trials.(5) Information for registered studies is generally entered into ClinicalTrials.gov by study sponsors or investigators, after which it undergoes a quality-control process before study information is made publicly available. Study information can be updated over time, and the registry includes a public audit trail of changes made to previously posted entries. Any human-subject clinical trial that is performed in accordance with local ethical and governmental regulations is eligible for registration with ClinicalTrials.gov.(6) Registration with ClinicalTrials.gov is required for most human-subject trials involving drugs or devices regulated by the US Food and Drug Administration that either are conducted in the United States, are conducted under an investigational new drug application or investigational device exemption, or involve the export of a drug or device manufactured in the US.(7)

Registry Search

We searched ClinicalTrials.gov on May 1, 2020 for trials registered after December 1, 2019 that tested interventions relevant to the COVID-19 pandemic. The search was performed using the following key words in the ClinicalTrials.gov "condition or disease" field: COVID-19 OR COVID OR SARS-CoV-2 OR coronavirus OR corona virus OR 2019-nCoV OR 2019 novel coronavirus OR severe acute respiratory syndrome coronavirus 2. We reviewed the individual registry entries for each of the studies identified by this search, and excluded those that did not meet the definition of a clinical trial adopted by the World Health Organization (WHO): any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health

outcomes.(8) Based on this definition we excluded observational studies, expanded access studies, and simulation or mannequin-based studies. We also excluded studies withdrawn prior to initiating enrollment and studies not relevant to COVID-19. We classified the remaining trials according to intervention type: drugs/biologics, vaccines, behavioral health or mental health interventions, physiologic interventions (e.g. prone positioning, ventilator settings), medical devices, and other interventions. Trials were included in more than one intervention category when relevant. Studies involving complementary or traditional medical interventions were included if they otherwise met the eligibility criteria described above.

Classification of Drug Trials

Those trials testing drugs or biologics were categorized according to the specific agents administered in each study. We grouped trials testing hydroxychloroquine or chloroquine together based on the similar structure and function of these drugs.(9) We considered trials to involve a particular drug or biologic if that specific drug/biologic was administered to participants in any of the trial's treatment arms as a part of the trial protocol. For trials with one treatment arm we considered a drug to be an intervention of interest if it was administered to all of the subjects in that study arm; for example, we did not consider hydroxychloroquine to be an intervention of interest if participants in a single-arm trial were permitted, but not required, to receive the drug. For trials with multiple treatment arms we considered a drug to be an intervention of interest if the study design facilitated an evaluation of the drug's efficacy by either administering it to participants in some but not all of the study arms, or by administering different doses or methods of administration to participants in different arms. We also distinguished between drug/biologic trials testing interventions for use in the treatment of patients with active COVID-19 disease from those testing interventions in a prophylactic capacity in order to prevent infection with COVID-19.

Data Collection and Reporting

We report key study design characteristics based on the registered information for each included trial. These characteristics include trial location(s), funder type(s), target enrollment number, intervention

model (single group, randomized, or sequential assignment), and anticipated primary completion date, which represents the date on which data collection is completed for the trial's primary outcome measure. Trials were classified as unblinded if participants were not masked to their assigned treatment group, single-blind if participants were masked to the group assignment and investigators were not, and double blind if both participants and investigators were masked to the group assignment. We also describe the subject recruitment status recorded as of May 1, 2020 for each trial. This reflects the recruitment status at the time of initial registration, or as of the most recent update to the registry record for entries that have been updated. Because the recruitment status field may not be updated immediately after the initiation of enrollment, we also report the number of trials for which the registered "Study Start Date" has passed. We also report the primary completion date for the included trials, which reflects the final date on which primary outcome data is generated for the final trial participant. We obtained counts for the total number of individuals worldwide confirmed to have COVID-19 from the WHO Coronavirus Disease Dashboard (https://covid19.who.int/).(10)

Data Analysis

We classified the included trials based on the category of intervention tested, and further classified trials of drugs or biologics based on the specific agent under investigation. Descriptive data are presented for each category, including proportions for categorical data and medians with interquartile ranges for continuous data. When relevant the number of registry entries with missing data is reported for each categorical variable. We compared proportions using chi-square tests, and p values <0.05 were considered significant. These analyses were performed using SPSS version 26.0 (SPSS Inc, Chicago, IL).

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this work.

RESULTS

Our search of ClinicalTrials.gov resulted in 1189 potentially eligible studies, 630 of which were clinical trials meeting our inclusion criteria (Figure 1). The majority of trials (n = 509, 81%) study drugs or biologic agents (Table 1). Twenty-six trials study physiologic interventions, most of which involve the study of mechanical ventilation strategies or prone positioning. There were 18 registered trials involving vaccines; seven of these involve testing the effects of tuberculosis or measles vaccines on COVID-19 susceptibility, and 11 test vaccines specifically designed for the SARS-CoV-2 virus.

Trial Design Characteristics

Among the trials testing drugs or biologic agents, 305 (60%) are designed as open-label studies (Table 2). Eight percent (n = 43) are single-blinded and less than one third (n = 161, 32%) mask both participants and investigators to the group assignment. Random allocation is used in 415 (82%) of the drug/biologic trials; 94 (18%) do not randomize participants.

Prophylaxis vs Treatment Trials

Among the 509 drug trials, 57 (11%) test the ability of the intervention to prevent COVID-19 infection, 452 (98%) test drugs in the context of treating active COVID-19 infections, and two trials include both prophylaxis and treatment arms. Based on current registry data, 40 of the prophylaxis trials (70%) involve the administration of hydroxychloroquine or chloroquine, and these 40 trials will enroll 88% of all prophylaxis trial participants. The proportion of trials utilizing randomization is similar between prophylaxis (88%) and treatment trials (81%), though prophylaxis trials are more likely to be double-blinded than treatment trials (54% vs 29%, p <.001).

Drugs Under Investigation

The drug/biologic trials involve the study of 218 unique agents; most of these are drugs which have been repurposed from other indications for study against COVID-19, as in the case of antimalarial treatments,

antiviral agents, and immunosuppressants.(11) The most commonly studied drugs are hydroxychloroquine or chloroquine, which are administered in 152 (30%) of the drug/biologic trials. Eighty-eight of these are treatment trials assessing hydroxychloroquine/chloroquine as a treatment of interest for COVID-19 patients, 38 study the prophylactic use of these drugs, two have both treatment and prophylactic arms, and 24 administer hydroxychloroquine/chloroquine as part of standard treatment to all participants in multi-arm studies. The total planned enrollment for the hydroxychloroquine/chloroquine trials is over 211,000 participants, which represents 65% of the total planned enrollment for all currently registered trials of drugs or biologics.

Azithromycin is administered in 53 trials, 47 (89%) of which also involve the administration of hydroxychloroquine or chloroquine. There are also 25 or more registered trials of convalescent plasma (n = 38), lopinavir/ritonavir (n = 30), stem cell treatments (n = 29), and tocilizumab (n = 25). Among these trials, the proportion with double-blinded designs ranges from 17% (lopinavir/ritonavir) to 34% (stem cell treatments). The proportion of studies utilizing randomized allocation ranges from 50% (convalescent plasma) to 93% (lopinavir/ritonavir).

Timing of Registration and Enrollment

Based on the most recent update to the ClinicalTrials.gov "Recruitment Status" field for each of the 630 included trials, 314 (50%) had not yet started enrollment, 287 (46%) were currently enrolling participants, and 16 (3%) had suspended or completed enrollment. As of May 1, 2020, review of each trial's registered "Study Start Date" and "Primary Completion Date," showed 534 trials (85%) that had passed the date on which recruitment was scheduled to begin but had not yet reached the anticipated primary completion date. The registered primary completion date had passed for 56 trials (9%). Analysis of the timing of registration for new interventional trials related to COVID-19 shows that 142 trials were registered in the first three months of 2020, and 488 trials were registered from April 1 to May 1(Figure 2). Discrepancies between data from the recruitment status field and the registered start and completion dates are likely to

reflect either delays in updating the recruitment status field after this status has changed, or a change in the trial schedule relative to the schedule anticipated at the time of registration. Ninety-eight trials (16%) are targeting completion by May 31, 2020, 244 (39%) by July 31, and 346 (55%) by September 30. For 173 trials (27%) the planned primary completion date is in 2021 or later.

DISCUSSION

As of May 1 2020, 630 trials had been registered with ClinicalTrials.gov to study interventions related to COVID-19 infection. Together these trials investigate 218 different drugs or biologic agents, though nearly one-third involve the study of hydroxychloroquine or chloroquine. Trials of hydroxychloroquine or chloroquine plan to enroll over 210,000 participants in total, which represents nearly two-thirds of the planned enrollment for all currently registered COVID-19-related trials assessing drugs or biologics. Additionally, azithromycin, convalescent plasma, lopinavir/ritonavir, and stem cells are each being studied in at least 25 trials. Many of these trials lack essential design features such as double blinding (absent in 68%) and randomized allocation of participants (absent in 18%) that are essential for using results to accurately estimate treatment effect.(11)

The data included in this analysis provide an overview of many of the initial clinical trials launched in response to the COVID-19 pandemic. Several important factors should be considered when interpreting these findings. First, while ClinicalTrials.gov is the largest trial registry in the world, many trials are either only listed in other registries or not registered at all, and there may be systematic study design differences between those trials registered with ClinicalTrials.gov and those that are not.(12-14) Despite this potential limitation, our dataset reflects a geographically diverse cohort of trials, including a large number of trials enrolling participants in both Europe and Asia. Similarly, while we utilized a comprehensive search strategy to find relevant trials within the ClinicalTrials.gov database, it is possible that this search failed to identify some relevant COVID-19 trials. Furthermore, it is also possible that

some of the currently registered trials will never be initiated. Finally, we present data reflecting registry entries for each of the included trials as of May 1, 2020. While some registry data-fields such as the chosen blinding strategy or the method of allocation are unlikely to change over time, others such as the recruitment status routinely change over the course of a trial. In some cases, updates to individual registry entries may be delayed, and the therefore data reflected in the public registry may be out of date.(15) For example, a number of the included trials had a recruitment status indicating that enrollment had not yet started, but the registered enrollment start date had passed. These discrepancies are likely to reflect either delays in updating the recruitment status field, or changes to a trial's enrollment schedule relative to what was anticipated at the time of registration.(16) Several near real-time online dashboards have been developed which provide both the research community and the public the ability to monitor characteristics, including recruiting status, of COVID-19 trials.(17, 18) These dashboards are valuable tools for tracking changes in the status of registered clinical trials over time, though they still rely on sponsors and investigators of the included trials to keep individual registry entries up to date.

Our results are consistent with other recently published studies that have characterized registered COVID-19 trials and have demonstrated that many of these trials are likely underpowered, and also lack design features such as randomized allocation and double blinding that are critical to generating bias-free estimates of treatment effects.(19, 20) Our findings build on this work by highlighting the proportion of trials of specific interventions that fail to utilize these design features. Additionally, we show that current plans call for over 210,000 individuals or nearly two-thirds of participants in all COVID-19 drug trials to be enrolled in trials assessing hydroxychloroquine or chloroquine. This includes 88% of all individuals enrolled in trials testing drugs for use in a preventative capacity. These findings demonstrate the substantial opportunity costs associated with a largely uncoordinated global trial response; resources spent enrolling massive numbers of participants in trials with suboptimal design features that are overwhelmingly focused on a few individual interventions like hydroxychloroquine would almost

certainly be better utilized conducting a smaller number of high quality trials aimed at testing other agents.

Our findings show a rapid increase in the number of trials registered starting in early April, approximately three weeks after the WHO declared COVID-19 a pandemic. These findings also indicate a profound lack of coordination of existing COVID-19 trials, which consequently increases the likelihood of wasted research effort and also poses risks.(21) Even under normal circumstances, clinical research often results in waste due to in part to inadequate power, suboptimal study design, and early termination.(2, 11, 22) Although attempting to confirm previously observed results through the replication of prior studies is important, the simultaneous conduct of numerous trials that test the same intervention is unlikely to be an optimally efficient allocation of research resources.(2) The problem of waste may be further exacerbated during the study of a pandemic disease in which 1) there exists limited relevant foundational research, 2) fluctuating case volumes make enrollment projections challenging, and 3) knowledge about the disease changes rapidly during the first few months, resulting in changes in regard to what is considered standard treatment.(23) For several of the drugs studied, the conduct of numerous small trials increases the risk for spurious findings which would add to confusion regarding treatment efficacy and might make it difficult for regulatory boards and clinicians to judge if there is clinical equipoise for larger trials.(24) Several of the included studies are directly competing for patients, increasing the risk that enrollment targets will not be met in a timely manner. Finally, performing pooled analyses may be challenging due to differences in inclusion criteria, dosing, and outcomes.(25-27) Centralized coordination of studies, particularly in the form of large-scale platform or adaptive trials, reduces the risk of bias and increases the potential to identify an effective treatment.(28, 29) The NIH ACTIV partnership is one such promising effort to improve trial coordination.(30) Other important initiatives aimed at addressing these concerns through the rapid implementation of large-scale, centrally coordinated COVID-19 trials are the Solidarity Trial,

sponsored by the WHO, and the Recovery Trial, sponsored by Oxford University, both of which have enrolled thousands of patients into multi-arm trials testing a number of different interventions.(31,32)

Further follow-up of the included trials through the results dissemination phase will ultimately help to assess the potential impact that these trials may have on clinical decision-making and patient outcomes.(33) Several COVID-19 related trials have already completed enrollment and results have been published.(34, 35) In particular, early trial data shows that remdesivir shortens the time to recovery among some hospitalized COVID-19 patients, and an open-label study of dexamethasone found evidence that steroid treatment decreases COVID-19 mortality.(36, 37) Results from many additional trials will be published over the coming months. Utilization of trial registry data will be critical to the interpretation of these results by helping the medical community assess for the presence of publication bias among this initial group of publications.(38, 39) This will be particularly important given that there are several interventions each being studied in a large number of trials. For example, if all 88 hydroxychloroquine/chloroquine trials defined a statistically significant result based on a two-sided p-value of 0.05, even in the absence of any true drug affect we would expect about 4 of these trials to report a statistically significant treatment effect due to chance alone.(24)

Our findings illustrate the potential for ClinicalTrials.gov and other registries to aid sponsors and investigators in reducing waste by informing design decisions for future COVID-19 trials. Specifically, in addition to utilizing study design features that help to produce unbiased estimates of treatment effects, key stakeholders should also utilize registry data to prioritize the conduct of trials that address important but relatively under-studied clinical questions. Additionally, there is evidence that outcome data are not available for a large number of previously completed trials utilizing drugs which are now under investigation for use in the treatment of COVID-19.(40) Given the potential relevance of patient safety information collected during the course of these prior trials to the treatment of COVID-19 patients,

regulators should work to secure public access to these trial datasets as a rapid and inexpensive way of utilizing trial registries to inform both COVID-19 research priorities and patient care decisions. Future assessment of COVID-19 trials including monitoring of enrollment rates, determining characteristics associated with early termination versus successful trial completion, and evaluating timely outcome reporting will help to inform policies aimed at increasing the value of trials for this and subsequent pandemic events.

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REFERENCES

1. Altman DG. The scandal of poor medical research. *BMJ*. 1994;308(6924):283-4.

2. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet*. 2014;383(9912):166-75.

3. Chavez C, Another wave of coronavirus will likely hit the US in the fall. Here's why and what we can do to stop it. CNN, May 2, 2020; https://www.cnn.com/2020/05/02/health/coronavirus-second-wave-fall-season/index.html.

4. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020 Apr 13. doi: 10.1001/jama.2020.6019.

5. Clinicaltrials.gov: Trends, Charts, and Maps: U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/resources/trends. Accessed May 11, 2020.

6. Clinicaltrials.gov: Submit Studies: U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/manage-recs. Accessed May 11, 2020.

7. Department of Health and Human Services. Clinical Trials Registration and Results Information Submission. Fed Regist. 2016; 81(183).

8. International Clinical Trials Registry Platform (ICTRP): World Health Organization. https://www.who.int/ictrp/en/. Accessed May 11, 2020.

9. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. *BMJ*. 2020;369:m1432.

10. WHO Coronavirus Disease (COVID-19) Dashboard: World Health Organization; 2020. Available from: https://covid19.who.int/. Accessed May 9, 2020.

11. Lythgoe MP, Middleton P. Ongoing Clinical Trials for the Management of the COVID-19 Pandemic. *Trends Pharmacol Sci*. 2020;41(6):363-382. doi:10.1016/j.tips.2020.03.006

11. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med*. 2012;157(6):429-38.

12. Hunter KE, Seidler AL, Askie LM. Prospective registration trends, reasons for retrospective registration and mechanisms to increase prospective registration compliance: descriptive analysis and survey. *BMJ Open*. 2018;8(3):e019983.

13. Loder E, Loder S, Cook S. Characteristics and publication fate of unregistered and retrospectively registered clinical trials submitted to The BMJ over 4 years. *BMJ Open*. 2018;8(2):e020037.

14. Tan AC, Jiang I, Askie L, Hunter K, Simes RJ, Seidler AL. Prevalence of trial registration varies by study characteristics and risk of bias. *J Clin Epidemiol.* 2019;113:64-74.

15. Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. *BMJ*. 2018;361:k1452.

16. Jones CW, Safferman MR, Adams AC, Platts-Mills TF. Discrepancies between ClinicalTrials.gov recruitment status and actual trial status: a cross-sectional analysis. *BMJ Open.* 2017;7(10):e017719.

17. Evidence-Based Medicine Datalab at the University of Oxford. COVID-19 Trials Tracker. http://covid19.trialstracker.net. Accessed August 18, 2020.

18. Cytel. Global Coronavirus COVID-19 Clinical Trial Tracker. https://www.covid-trials.org. Accessed August 18, 2020.

19. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical trials assessing treatments for COVID-19: a cross-sectional analysis. *BMJ Open*. 2020;10(6):e039978. Published 2020 Jun 9. doi:10.1136/bmjopen-2020-039978

20. Huang J, He Y, Su Q, Yang J. Characteristics of COVID-19 Clinical Trials in China Based on the Registration Data on ChiCTR and ClinicalTrials.gov. *Drug Des Devel Ther*. 2020;14:2159-2164. Published 2020 May 29. doi:10.2147/DDDT.S254354

21. Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. *Lancet*. 2014;383(9912):156-65.

22. Ioannidis JP. Clinical trials: what a waste. *BMJ*. 2014;349:g7089.

23. Klitzman R. Evolving Challenges and Research-Needs Concerning Ebola. *Am J Public Health*. 2015;105(8):1513-5.

24. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. 2017;46(2):746-55.

25. Bangdiwala SI, Bhargava A, O'Connor DP, et al. Statistical methodologies to pool across multiple intervention studies. *Transl Behav Med*. 2016;6(2):228-35.

26. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J*. 2014;35(47):3336-45.

27. Halpern SD, Karlawish JH, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA*. 2002;288(3):358-62.

28. Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov*. 2019;18(10):797-807.

29. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*. 2015;313(16):1619-20.

30. NIH to launch public-private partnership to speed COVID-19 vaccine and treatment options: National Institutes of Health. https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options. Accessed April 26, 2020.

31. ISRCTN Registry. Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients. http://www.isrctn.com/ISRCTN83971151. Accessed August 16, 2020.

32. ClinicalTrials.gov. Randomised Evaluation of COVID-19 Therapy (RECOVERY). https://clinicaltrials.gov/ct2/show/NCT04381936

33. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet*. 2014;383(9913):267-76.

34. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 2020;3(4):e208857.

35. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382(19):1787-99.

36. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med*. 2020;NEJMoa2007764. doi:10.1056/NEJMoa2007764

37. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med*. 2020;NEJMoa2021436. doi:10.1056/NEJMoa2021436

38. Song SY, Koo DH, Jung SY, Kang W, Kim EY. The significance of the trial outcome was associated with publication rate and time to publication. *J Clin Epidemiol*. 2017;84:78-84.

39. DeVito NJ, Goldacre B. Catalogue of bias: publication bias. *BMJ Evid Based Med*. 2019;24(2):53-4.

40. Rodgers F, Pepperrell T, Keestra S, Pilkington V. Missing clinical trial data: the knowledge gap in the safety of potential COVID-19 drugs. medRxiv. June 3, 2020. Doi: https://doi.org/10.1101/2020.05.30.20117523

Table 1: Characteristics of COVID-19 related clinical trials registered with ClinicalTrials.gov from December 1, 2019 to April 19, 2020.

Trial Characteristics	All Trials (n = 630)
Enrollment Status, No. (%)	
Not yet recruiting	314 (50)
Recruiting	287 (46)
Active, not recruiting	13 (2)
Enrollment completed	11 (2)
Stopped early/suspended	5 (1)
Intervention, No. (%)[a]	
Drug/biologic	509 (81)
Behavioral/mental health	28 (4)
Physiologic	26 (4)
Device	28 (4)
Vaccine[b]	18 (3)
Other	27 (4)
Funding Source, No. (%)[a]	
Industry	143 (23)
NIH[c]/US government	11 (2)
Other/none	558 (89)
Location[a]	
Europe	215 (34)
United States	192 (30)
China	74 (12)
Other Asia	56 (9)
Other	89 (14)
Not specified	24 (4)
Number of participants, median (IQR)	150 (60-401)

[a] Trials may be listed in more than one category; totals therefore add to more than 100%.
[b] Includes seven vaccine trials that study the effect of tuberculosis or measles vaccines on the incidence of COVID-19 infection rather than a vaccine specific to the novel coronavirus.
[c] National Institutes of Health

Table 2: Characteristics of registered COVID-19 trials assessing drugs or biologic agents.

Trial Characteristics	All Drugs/ Biologics (n = 509)	HCQ Treatment[a,b] (n = 90)	HCQ Prophylaxis[a] (n = 40)	Convalescent Plasma (n = 38)	Lopinavir/ Ritonavir (n = 30)	Stem Cells (n = 29)
Trial phase, n (%)[c]						
Phase I	34 (7)	5 (6)	1 (3)	6 (16)	0	8 (28)
Phase II	202 (40)	25 (28)	10 (25)	17 (45)	7 (23)	17 (59)
Phase III	183 (36)	46 (51)	24 (60)	7 (18)	13 (43)	3 (10)
Phase IV	43 (8)	11 (12)	1 (3)	0	6 (20)	0
Other/Not specified	47 (9)	3 (3)	4 (10)	8 (21)	4 (13)	1 (3)
Allocation method, n (%)						
Randomized	415 (82)	79 (88)	36 (90)	19 (50)	28 (93)	19 (66)
Non-randomized	94 (18)	11 (12)	4 (10)	19 (50)	2 (7)	10 (34)
Number of trial arms, n (%)						
Single	74 (15)	10 (11)	2 (5)	17 (45)	0	8 (28)
Multiple	435 (85)	80 (89)	38 (95)	21 (55)	30 (100)	21 (72)
Blinding, n (%)						
Open label	305 (60)	58 (64)	12 (30)	28 (74)	23 (77)	17 (59)
Single (participant)	43 (8)	10 (11)	5 (13)	2 (5)	2 (7)	2 (7)
Double (participant and investigator)	161 (32)	22 (24)	23 (58)	8 (21)	5 (17)	10 (34)
Prophylaxis trial, n (%)	57 (11)	2 (2)[d]	40 (100)	1 (3)	3 (10)	2 (7)
Number of participants, median (IQR)	150 (60-413)	400 (148-655)	825 (374-1729)	85 (20-235)	250 (80-550)	30 (20-78)

[a] Includes trials of hydroxychloroquine or chloroquine.
[b] Azithromycin trials (n = 53) not listed as 47 of these also involve hydroxychloroquine or chloroquine.
[c] Phase I/II trials classified as phase II, phase II/III trials classified as phase III.
[d] Two hydroxychloroquine trials included both treatment and prophylaxis arms.

Figure 1. Flowchart of included trials.

Figure 2: Timeline describing the registration and conduct of COVID-19 clinical trials along with the global total of confirmed COVID-19 cases.

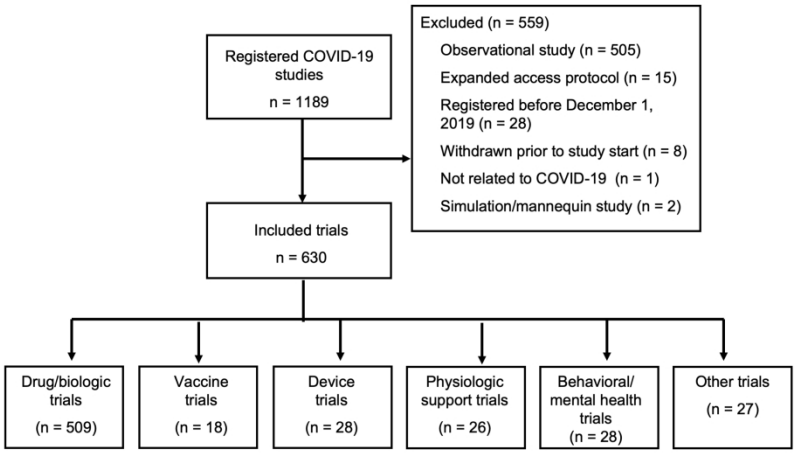

Figure 1. Flowchart of included trials.

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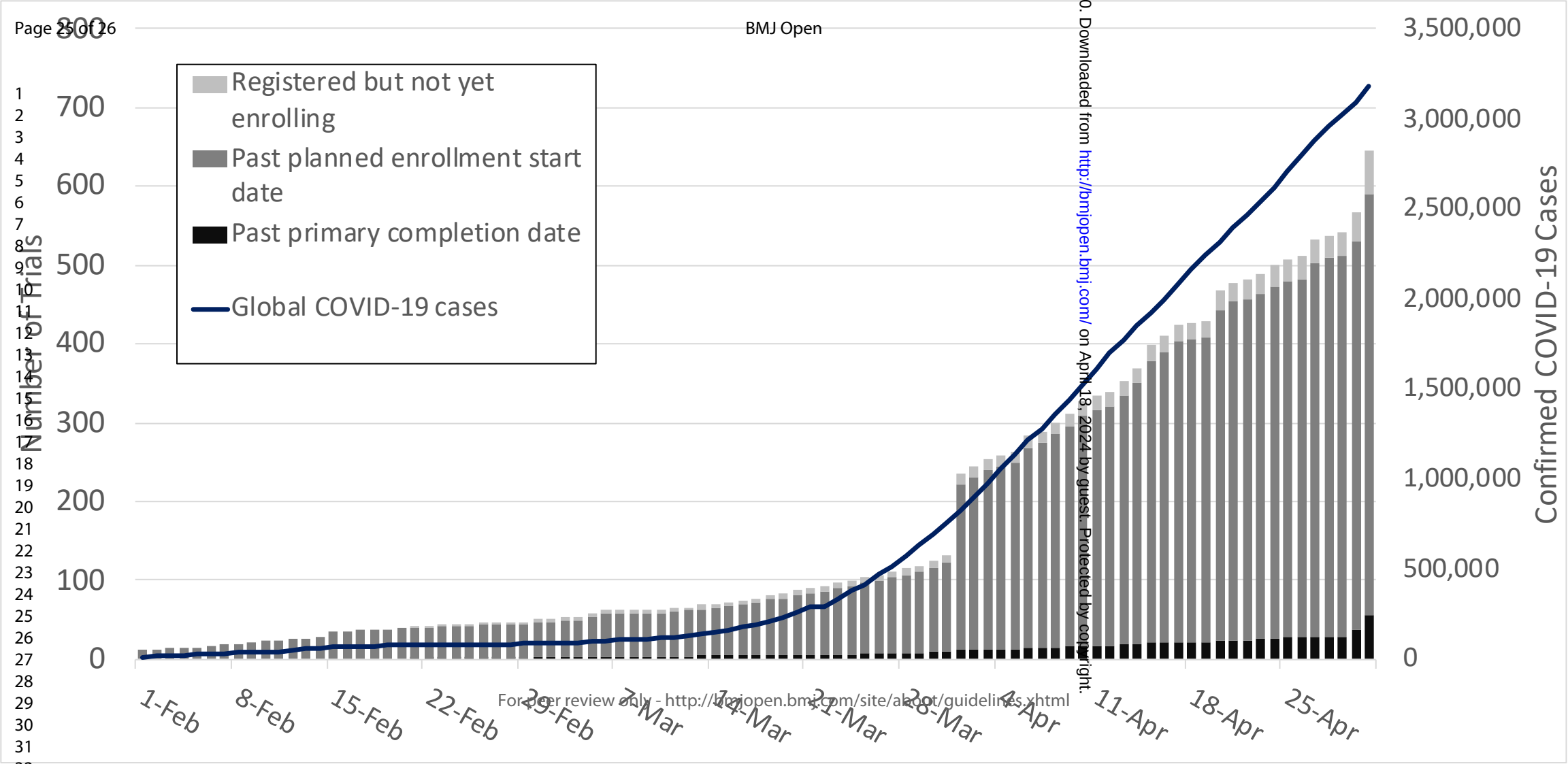

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1,2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	None

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.