

Analysis of the WHO ICTRP for novel coronavirus clinical trial registrations

Gao Song, MD^{a,*}, Meng Qun Cheng, MD^b, Xian Wen Wei, MD^c

Abstract

Up-to-date information on the current progress made in the research and development to control the global COVID-19 pandemic is important. The study aimed to analyze the clinical trial characteristics and vaccine development progress of the new Coronavirus Disease 2019 (COVID-19) registered with the World Health Organization International Clinical Trial Registry Platform (WHO ICTRP).

A comprehensive search of COVID-19 clinical trials since the establishment of the ICTRP to June 11, 2020, was conducted to record and analyze relevant characteristics. Chi-Squared test was used to compare the statistical differences between different research types, interventions, and sources.

A total of 3282 COVID-19 clinical trials in 17 clinical trial registration centers were registered with the WHO ICTRP. The main research sources for the present study were ClinicalTrials.gov and ChiCTR. There were significant differences in the parameters of study location ($P=.000$), number of participants ($P=.000$), study duration ($P=.001$), research stage ($P=.000$), randomization procedure ($P=.000$), and blinding method ($P=.000$) between the 2 registration sources. There were significant differences in all the parameters between different kinds of intervention methods. Hydroxychloroquine, plasma therapy, and Xiyanping injection were the high-frequency research drugs used. Ten different vaccine studies were registered under phases I-II.

Amongst the studies researched, heterogeneity existed for various parameters. Differences in the type of study, interventions, and registration sources of the studies led to significant differences in certain parameters of the COVID-19 clinical trials. The statistics of high-frequency drugs and the progress of vaccine trials may provide an informative reference for the prevention and control of COVID-19.

Abbreviations: ANZCTR = Australia New Zealand Clinical Trials Australian New Zealand Clinical Trials Registry, COVID-19 = Corona virus disease 2019, ChiCTR = China Clinical Trial Registry, EUCTR = EU Clinical Trials Register, GCTR = German Clinical Trials Register, ICTRP = International Clinical Trials Registry Platform, IRCT = Iran Clinical Trials Registry, ISRCTN = British International Standard Random Register of Controlled Trial Numbers, JPRN = Japan Primary Registries Network, PHEIC = Public Health Emergency of International Concern, NCP = Novel coronavirus pneumonia, NTR = Netherlands Trial Register, TCTR = Thai Clinical Trials Registry.

Keywords: high frequency drug research, novel coronavirus (COVID-19), registered clinical trials, SARS-CoV-2, vaccine, WHO ICTRP

1. Introduction

Since the 1970s, more than 30 new types of infectious diseases such as the Ebola virus disease, human infection with the highly pathogenic avian influenza, and Zika virus disease have appeared in China, seriously threatening the public health security.^[1,2]

In December 2019, there were multiple cases of unexplained pneumonia in Wuhan, which were subsequently confirmed to be caused by a new coronavirus. The World Health Organization (WHO) named the disease caused by the new coronavirus as COVID-19 (Coronavirus disease 2019) on February 11, 2020,

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MQC and XWW contributed equally to this work.

This study aimed to analyze the characteristics of the clinical trials and the progress of the vaccine development programs for the new coronavirus (Coronavirus Disease 2019, COVID-19) registered with the World Health Organization International Clinical Trial Registry Platform (WHO ICTRP).

Since all the data used in the evaluation of this study has been published, the study does not require ethical endorsement and will be reported in peer-reviewed journals.

The authors declare that they have no competing interests.

The datasets generated during and/or analyzed during the current study are publicly available.

^a Department of Pharmacy, Pu'er People's Hospital, ^b Department of Reproductive Medicine, The Pu'er People's Hospital, ^c Department of Neurology, Puer People's Hospital, Yunnan, China.

* Correspondence: Gao Song, Department of Pharmacy, The Pu'er People's Hospital of Yunna, 44 Zhenxing Rd., Puer 665000, China (e-mail: 387925693@qq.com)

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while the International Virus Classification Committee officially named the original 2019 new coronavirus (2019-nCoV) as SARS-CoV-2.^[3] On January 30, 2020, WHO declared the Novel Coronavirus outbreak as a Public Health Emergency of International Concern (PHEIC).^[4]

At present, COVID-19 has spread worldwide. On March 11, 2020, WHO announced that COVID-19 constitutes a pandemic.^[5] As of June 11, 2020, the cumulative number of diagnoses worldwide exceeded 7.6 million and the number of deaths exceeded 400000. The rapid spread of the pandemic worldwide has raised serious public health concerns. Promptly carrying out clinical drug research and promoting the sharing of clinical trial information is essential to prevent and control the spread of the pandemic. At present, domestic and foreign scholars are actively involved in clinical trials and research with the focus on diagnosis, treatment, and vaccine development to establish prevention and control methods. A prompt discussion on the current status of research and development in this field is of great significance for accelerating the development and transformation of results in this field. Therefore, this study comprehensively analyzes the registrations of global COVID-19 clinical trials and provides a useful information reference for curbing the spread of the COVID-19 pandemic.

2. Methods

2.1. Data collection

The “COVID-19 Clinical Research Index” issued by the ICTRP Center (Including the ClinicalTrials.gov and ChiCTR) database were searched with the keywords “Novel coronavirus” or “2019-nCoV” or “COVID-19” or “SARS-CoV-2” for trials registered till June 11, 2020. The following information was extracted from the 2 databases:

1. Registration status (date of registration, date of completion, the region of registration, etc.),
2. source of funding,
3. recruitment status,
4. ethical approval,
5. data management committee,
6. research type,
7. research design,
8. research stage,
9. time limit of the study,
10. number of participants,
11. intervention methods,
12. settings for the blinding,
13. data sources.

Two reviewers (Gao Song and Mengqun Cheng) transferred the data to SPSS, quality checked, and analyzed the final dataset. There was no disagreement between the 2 reviewers on the final dataset of 3282 studies.

2.2. Definitions

The primary research characteristics were identified as the research type, intervention method, and the registration platform. The type of research was categorized as intervention, observation, and others (e.g., prevention, diagnostic test, and prognosis research). The intervention method was categorized as:

1. Chemical treatment (CMT),

2. Biologics and immunoregulatory (BI) drugs such as cell therapy, antibodies, and glucocorticoid,
3. Traditional Chinese medicine (TCM) such as Chinese herbal medicine, proprietary Chinese medicines,
4. Prevention and Control Research (PCR) such as cognitive, attitude and behavioral interventions, sports and psychotherapy, environmental protection, prevention, and control, etc.,
5. No intervention (missing information or not applicable [NA]).

The research stage was categorized as

1. early stage (stage 0, I, I/II, II),
2. late-stage (stage III or IV), and
3. non-applicable.

The study design characteristics included

1. the number of study locations: single study location or multiple study locations;
2. the number of participants: ≤ 100 , 100 to 1000, and > 1000 ;
3. the study duration (month): ≤ 3 , 3 to 12, and > 12 ;
4. the blinding method: open, blind, and unspecified;
5. study assignment: randomized, non-randomized, and others (e.g., factorial grouping, continuous grouping);

2.3. Ethics statement

All the data used in the evaluation of this study has been published, thus no ethical approval and patient consent are required.

2.4. Statistical analyses

The data is presented in the form of a descriptive analysis of the source and number of registrations of COVID-19 clinical studies. The study duration was calculated based on ICTRP’s “study execution time”. Chi-square test was performed at 95% significance level to test the significance of the difference for research type, intervention methods, and design characteristics between the 2 research sources. Chi-Squared test was performed only for the main features while excluding certain features from the analysis. For example, because 100.0% of the 3282 studies had key inclusion/exclusion criteria, the item was excluded from the Chi-Squared test. IBM SPSS version 22.0 software was used for statistical analyses. A *P* value of less than .05 was considered statistically significant.

3. Results

3.1. ICTRP registration of COVID-19 clinical trials

A total of 3282 COVID-19 clinical trials in 17 clinical trial registration centers were registered with the WHO ICTRP. The main sources of registered clinical trials were ClinicalTrials.gov (56.28%, *N*=1847) and ChiCTR (21.48%, *N*=705). The registration source and country are shown in Table 1.

3.2. COVID-19 clinical trial registrations

3.2.1. Basic characteristic. As shown in Table 2, interventional studies and observational studies accounted for 1240 (37.78%) and 1936 (58.99%) of the COVID-19 clinical trials, respectively. CMT, treatment with BI, TCM, and PCR accounted for 39.85%, 13.65%, 7.01%, and 7.89% of the interventions, respectively. The main clinical outcome evaluation indicators

Table 1**Sources of COVID-19 registered clinical trials.**

Registration platform	Number of registrations	Web of address	Main Countries
ClinicalTrials.gov	1847	https://clinicaltrials.gov	68 countries including United States, Italy, China, Canada, France, Spain, etc.
ChiCTR	705	http://www.chictr.org.cn	China
EU Clinical Trials Register	194	https://www.clinicaltrialsregister.eu	France, Norway, Netherlands, Germany
IRCT	171	http://en.irct.ir/trial	Iran
German Clinical Trials Register	80	http://www.drks.de	Germany
CTRI	67	http://www.ctri.nic.in/Clinicaltrials	India
ISRCTN	51	http://isrctn.com	United Kingdom, Canada, Germany
ANZCTR	51	https://anzctr.org.au	Australia
Netherlands Trial Register	38	https://trialregister.nl	The Netherlands
JPRN	31	https://jrct.niph.go.jp	Japan
RPCEC	14	https://rpcec.sld.cu/en/trials	Cuba
REBEC	10	http://www.ensaioclinicos.gov.br	Brazil
TCTR	13	http://www.clinicaltrials.in.th	Thailand
PACTR	6	https://pactr.samrc.ac.za	Egypt
CRIS	2	http://cris.nih.go.kr	Korea
LBCTR	2	http://lbctr.moph.gov.lb	Lebanon
SLCTR	1	https://slctr.lk/trials	Sri Lanka

were summarized into 2 aspects: laboratory indicators/viral nucleic acid negative evaluation (N=1770, 53.93%) and disease progression/symptom evaluation (N=1108, 33.76%). Of the total studies, 48.81% were recruiting subjects, 86.50% of the studies had passed the ethical review, and all the studies had key inclusion and exclusion criteria.

Table 2**Basic characteristics of COVID-19 registered clinical trials.**

	N=3282	N(%)
Type of Study		
Interventional	1240	37.78%
Observational	1936	58.99%
others	106	3.23%
Intervention model		
CMT	1299	39.58%
BI	448	13.65%
TCM	230	7.01%
PCR	259	7.89%
others	1046	31.87%
Registration platform		
ClinicalTrials.gov	1847	56.28%
ChiCTR	705	21.48%
others	730	22.24%
Primary outcome		
Evaluation of viral nucleic acid conversion/Laboratory index	1770	53.93%
Disease progression/Symptom evaluation	1108	33.76%
others	404	12.31%
Recruiting status		
Actively recruiting	1602	48.81%
Authorised	190	5.79%
Not yet open for recruitment	1491	45.43%
Ethical approval		
Yes	2839	86.50%
Data Management Committee		
Yes	2430	74.04%

1. Evaluation of viral nucleic acid turning negative is the time and ratio of viral nucleic acid turning negative; laboratory indicators were chest CT, inflammation indicators, lung function, blood routine, liver and kidney function. 2. Disease progression is mortality, hospitalization time, aggravated time to ICU, mechanical ventilation or oxygen therapy time, disease severity; symptom evaluation is clinical symptom relief, Body temperature recovery time, TCM syndromes.

3.2.2. Design features. As shown in Table 3, most of the studies were single-center (N=2893, 88.15%) with multi-center studies accounting for 11.85% of the studies; the number of participants was concentrated in the 2 groups of ≤ 100 (N=1278, 38.94%) and 100-1000 (N=1432, 43.63%); most of the studies were completed within 4-12 months (N=1302, 39.67%); 27.51% of the studies were in the early stage (0, I, II) while 40.01% of the studies were in the late stage (III, IV); 43.97% of the studies had adopted a randomly assigned design method; only 16.15% of the studies were blinded.

3.2.3. Heterogeneity analysis of study design features. As shown in Table 4, chi-square test revealed significant differences in the design characteristics depending on the type of study, for the number of participants ($P=.000$), study duration ($P=.000$), the stage of study ($P=.000$), the randomization procedure ($P=.000$), and the blinding method ($P=.000$). Intervention and observational studies accounted for 10.16% and 11.11% of the multi-center studies, respectively; there was no significant difference in their design characteristics ($P=.402$). For the intervention studies, the Chi-Squared test showed significant differences in all the design features of the 4 intervention methods of CMT, BI, TCM, and PCR. For the 2 main registration sources of ClinicalTrials.gov and ChiCTR, the Chi-Squared test showed that the design characteristics namely multi-center study ($P=.000$), number of participants ($P=.000$), study duration ($P=.000$), research stage ($P=.000$), and blinding method ($P=.000$) showed significant differences. ClinicalTrials.gov and ChiCTR accounted for 48.13% and 44.26% of the randomization studies, respectively; there were no significant differences in their design characteristics ($P=.214$).

3.3. COVID-19 drug research frequency statistics and vaccine development

3.3.1. High-frequency research statistics. Table 5 shows the top 3 drugs used in CMT, BI, and TCM. In CMT, hydroxy-chloroquine was used by 284 studies (21.86%), followed by lopinavir/ritonavir [105 studies (8.08%)], and azithromycin [80 studies (6.16%)]. In BI, plasma treatment was used in 128 studies (28.57%), followed by tocilizumab [58 studies (12.95%)], and

Table 3
Design features of COVID-19 registered clinical trial.

	N = 3282	N (%)
Number of study locations		
Single study location	2893	88.15%
Multiple study locations	389	11.85%
Participant number		
≤100	1278	38.94%
100~1000	1432	43.63%
> 1000	554	16.88%
N/A	18	0.55%
Study period(MO)		
≤3	934	28.46%
3~12	1302	39.67%
>12	735	22.39%
N/A	311	9.48%
Stage of Study		
Early stage(< =2)	903	27.51%
Late stage(> =2/3)	1313	40.01%
Not applicable stage	1066	32.48%
Study Assignment		
Randomized	1443	43.97%
Nonrandomized	581	17.70%
others	1258	38.33%
Blind method		
Open	1267	38.60%
Blinding	530	16.15%
N/A	1485	45.25%
Key inclusion/exclusion criteria		
Yes	3282	100.00%

stem cell treatment [37 studies (8.26%)]. In TCM, Xi Yanping, Qingfei detox soup, and Lianhua Qingwen capsules were the most frequently studied drugs. In BEI research, behavioral intervention, psychological intervention, and natural environment research were most popular.

3.3.2. COVID-19 clinical trial vaccine development. As shown in Table 6, a total of 10 related vaccine studies were registered in the ICTRP: Inactivated virus vaccine (China/ChiCTR2000031809, china/ChiCTR2000032459, China/CNCT04352608), Adenovirus vector vaccine (China/NCT04313127, Canada/NCT04398147, China/NCT04341389), Subunit vaccine (Australia/NCT04405908), Nucleic acid vaccine (DNA + mRNA) (America/NCT04336410, America/NCT04283461, America/NCT04368728).

4. Discussion

The importance of clinical trial information sharing in a pandemic situation

In clinical trials, information sharing is the key to accelerated conversion of clinical resources and promoting scientific breakthroughs.^[6] The WHO ICTRP clinical trial registration and sharing mechanism play an important role in achieving transparency of clinical trial information.^[7] After facing a public safety crisis, the registration of clinical trial programs realized the importance of transparency of clinical trials to a certain extent and the need to share information promptly. This also provides real-time guidance in preventing and controlling the spread of the pandemic and evaluating the trends of the pandemic and the effects of intervention measures.^[8] COVID-19's "pandemic

prevention and control" strategy is closely related to important measures to improve the transparency of clinical trials in terms of sharing original data of the subjects and standardized trial design, registration, and implementation.^[9,10]

4.1. Normative and complete registration information

The standardization and completeness of clinical trial information and data acts as an assurance for improving the quality of clinical trials and is also a prerequisite for transparency. This can effectively reduce the wastage of research resources, publication bias, the selective bias in reporting the data, as well as promote good communication.^[11] Based on the analysis of the COVID-19 registration trials, the ChiCTR registration guide divides the study types into 7 categories: interventional studies, preventive studies, diagnostic tests, prognostic studies, and observational studies, etc.^[12] However, its registration guidelines are unclear in classifying research according to the nature and purpose of the research. Based on the international standards, the classification of interventions and observations may be clearer.^[13] The registration information of clinical trials of related traditional Chinese medicines in ClinicalTrials.gov is not standardized and uniform and includes various types of Chinese medicines like soups (Tang, decoction, soup), pills (wan, pill), etc. Other common problems include unclear research types, unknown methods of blinding in the research design, large differences in the outcome evaluation indicators, as well as irregular expressions and unreasonable selection of indicators. It is worth noting that 14.50% of the studies have not passed the ethical review and the WHO ICTRP has requested the registration unit to review the supplementary information. Medical ethics review should strictly abide by the "ethical review methods of biomedical research involving humans".^[14] Some non-standard registration behaviors have reduced the quality of information sharing in COVID-19 clinical trials and the establishment of a core indicator set for COVID-19 (COS-COVID) as soon as possible may solve such obstacles.^[15]

4.2. Attention to the scientificity and feasibility of the experimental design

Judging from the registered COVID-19 trial designs, most of the studies are interventional studies and are based on randomized design features. Randomized controlled trials (RCTs) adopt the principle of randomization and control to effectively eliminate most confounding factors and therefore are the gold standard of current clinical trials. However, COVID-19, as a new infectious disease, has high pathogenicity and infectivity. The science and feasibility of whether pandemic prevention and control is the preferred test design method for COVID-19 RCTs may need further consideration. It can be seen from the research results that there are heterogeneities between different parameters of different research design features indicating that the selection of research design methods needs to be more closely integrated with the practical clinical issues. For the exploration of the epidemiological and clinical features, observational studies with well-designed trials may also provide sufficient evidence-based results for the investigation of the causal effects; the design features of such studies are also more appropriate.^[16]

The highest number of registrations for COVID-19 trials are in phases III and IV, which may be because most clinical trials are researched in the form of "old drugs" and new methods, mainly

Table 4

Design characteristic differences among Basic characteristics of COVID-19 registered clinical trials.

	Type of Study				Intervention model				Registration platform				
	Interventional (n = 1240)		Observational (n = 1936)		P value(χ^2)	CMT (n = 1299)	BI (n = 448)	TCM (n = 230)	PCR (n = 259)	P value(χ^2)	ClinicalTrials.gov (n = 1847)	ChiCTR (n = 705)	P value(χ^2)
Number of study locations	1114 (89.84%)	1721 (88.89%)	.402 ($\chi^2 = 0.703$)	1180 (90.84%)	376 (83.93%)	167 (72.61%)	220 (84.94%)	1643 (88.96%)	557 (79.01%)	.000* ($\chi^2 = 42.466$)	1643 (88.96%)	557 (79.01%)	.000* ($\chi^2 = 42.466$)
Single study location	126 (10.16%)	215 (11.11%)		119 (9.16%)	72 (16.07%)	63 (27.39%)	39 (15.06%)	204 (11.04%)	148 (20.99%)		204 (11.04%)	148 (20.99%)	
Multiple study locations	601 (48.47%)	810 (41.84%)	.000* ($\chi^2 = 25.057$)	514 (39.57%)	204 (45.54%)	116 (50.43%)	145 (55.98%)	883 (47.81%)	331 (46.95%)	.000* ($\chi^2 = 119.134$)	883 (47.81%)	331 (46.95%)	.000* ($\chi^2 = 66.314$)
Participant number	413 (33.31%)	807 (41.68%)		660 (50.81%)	166 (37.05%)	55 (23.91%)	81 (31.27%)	837 (45.32%)	253 (35.89%)		837 (45.32%)	253 (35.89%)	
$\leq 10^2$	223 (17.98%)	308 (15.91%)		123 (9.47%)	75 (16.74%)	56 (24.35%)	28 (10.81%)	120 (6.50%)	115 (16.31%)		120 (6.50%)	115 (16.31%)	
$10^2 \sim 10^3$	3 (0.24%)	11 (0.57%)		2 (0.15%)	3 (0.67%)	3 (1.30%)	5 (1.93%)	7 (0.38%)	6 (0.85%)		7 (0.38%)	6 (0.85%)	
> 10^3	570 (45.97%)	350 (18.08%)	.000* ($\chi^2 = 395.440$)	341 (26.25%)	112 (25.00%)	109 (47.39%)	155 (59.85%)	499 (27.02%)	229 (32.48%)	.001* ($\chi^2 = 311.143$)	499 (27.02%)	229 (32.48%)	.001* ($\chi^2 = 17.456$)
N/A	488 (39.35%)	788 (40.70%)		430 (33.10%)	144 (32.14%)	70 (30.43%)	66 (25.48%)	639 (34.60%)	253 (35.89%)		639 (34.60%)	253 (35.89%)	
Study duration (MO)	105 (8.47%)	620 (32.02%)		431 (33.18%)	73 (16.29%)	32 (13.91%)	18 (6.95%)	479 (25.93%)	170 (24.11%)		479 (25.93%)	170 (24.11%)	
≤ 3	77 (6.21%)	178 (9.19%)		97 (7.47%)	119 (26.56%)	19 (8.26%)	20 (7.72%)	230 (12.45%)	53 (7.52%)		230 (12.45%)	53 (7.52%)	
3~12	413 (33.31%)	481 (24.85%)	0.000* ($\chi^2 = 120.533$)	58745.19 (%)	76 (16.96%)	74 (32.17%)	66 (25.48%)	579 (31.35%)	175 (24.82%)	0.000* ($\chi^2 = 262.409$)	579 (31.35%)	175 (24.82%)	0.000* ($\chi^2 = 15.716$)
> 12	353 (28.47%)	930 (48.04%)		295 (22.71%)	166 (37.05%)	67 (29.13%)	162 (62.55%)	736 (39.85%)	277 (39.29%)		736 (39.85%)	277 (39.29%)	
N/A	474 (38.23%)	525 (27.12%)		417 (32.10%)	206 (45.98%)	89 (38.70%)	31 (11.97%)	532 (28.80%)	253 (35.89%)		532 (28.80%)	253 (35.89%)	
Stage of Study	531 (42.82%)	870 (44.94%)	0.000* ($\chi^2 = 48.571$)	512 (39.41%)	231 (51.56%)	133 (57.83%)	131 (50.58%)	889 (48.13%)	312 (44.26%)	0.000* ($\chi^2 = 105.115$)	889 (48.13%)	312 (44.26%)	.214 ($\chi^2 = 3.079$)
Early stage (< = 2)	150 (12.10%)	388 (20.04%)		238 (18.32%)	87 (19.42%)	67 (29.13%)	67 (25.87%)	372 (20.14%)	153 (21.70%)		372 (20.14%)	153 (21.70%)	
Late stage (> = 2/3)	559 (45.08%)	678 (35.02%)		549 (42.26%)	130 (29.02%)	30 (13.04%)	61 (23.55%)	586 (31.73%)	240 (34.04%)		586 (31.73%)	240 (34.04%)	
Not applicable stage	454 (36.61%)	783 (40.44%)	0.000* ($\chi^2 = 53.408$)	671 (51.66%)	134 (29.91%)	53 (23.04%)	89 (34.36%)	673 (36.44%)	134 (19.01%)	0.000* ($\chi^2 = 222.734$)	673 (36.44%)	134 (19.01%)	0.000* ($\chi^2 = 71.719$)
Randomization procedure	275 (22.18%)	240 (12.40%)		165 (12.70%)	48 (10.71%)	77 (33.48%)	87 (33.59%)	331 (17.92%)	159 (22.55%)		331 (17.92%)	159 (22.55%)	
Randomized	511 (41.21%)	913 (47.16%)		463 (35.64%)	266 (59.38%)	100 (43.48%)	83 (32.05%)	843 (45.64%)	412 (58.44%)		843 (45.64%)	412 (58.44%)	
Nonrandomized													
others													
Blind method													
Open													
Blinding													
N/A													

The blind method includes single blind, double blind, triple blind, and quad blind.

Table 5
Statistics of research frequency in COVID-19 clinical trials.

Type of intervention	Metabolic intervention	Research frequency	N (% of Intervention type)
CMT	Hydroxychloroquine	284	21.86%
	Lopinavir/Ritonavir	105	8.08%
	Azithromycin	80	6.16%
BI	Plasma	128	28.57%
	Tocilizumab	58	12.95%
	Stem cell	37	8.26%
TCM	Lianhua Qingwen Capsule	5	2.17%
	Qingfei Detox Soup	4	1.74%
	Xi Yanping	3	1.30%
BEI	Behavior Research	84	32.43%
	Psychological research	41	15.83%
	Natural environment	18	6.95%

discussing the effectiveness of drugs within the safe dose range for COVID-19. There are 76 clinical trials in phase I/II and 131 in phase II/III. The research method used is the adaptive seamless design (ASD).^[17] ASD has been widely used in the development of drugs for cancer, cardiovascular, and other systems, which can shorten the development cycle and reduce costs.^[18] The use of ASD in the development of COVID-19 targeted drugs may show effects that are the need of the hour in the present situation where disease prevention as well as controlling the pandemic are crucial.

Further, COVID-19 clinical trial designs should give priority to “timeliness”. Reasonable and timely drug development is very important for the prevention and control of the pandemic, and its timeliness has social significance. It can be seen from the statistics that about 1/3rd of the clinical trial research time is concentrated between 3 to 12 months. Also, the clinical trial sample size needs to consider the balance between clinical and statistical significance such that the numbers reflect the reliability and repeatability of the research results. Although large-scale RCT research is more clinically significant, considering the timeliness, it may be appropriate to concentrate the number of participants recruitment in 2 ranges of ≤ 100 and 100-1000 cases. Designing a study with a reasonable number of recruitments and research cycles, while ensuring the quality of clinical trials, can also effectively improve the transformation of clinical trial outcomes; this is of great significance for the prevention and control of the pandemic.

4.3. Analysis of high-frequency intervention measures

In the trial registrations, the main intervention methods include drug treatment and prevention and control intervention. In the medical treatment with TCM comprises of all kinds of Chinese herbal medicine compounds and the use of Chinese patent medicines such as Lianhua Qingwen, Xianping injection, etc. Medicine treatment mainly includes

1. antiviral drug treatment, such as Remdesivir, hydroxychloroquine, etc.;
2. targeted host drugs, such as immunoglobulin, mesenchymal stem cells, plasma treatment, etc., that can improve patient immunity and prevent autoimmunity related sexual damage (against the immune storm caused by cytokines).

Most of these drugs have been used *in vitro* or *in vivo* or previous SARS and MERS coronaviruses.^[19,20]

Hydroxychloroquine is one of the most frequently studied drugs. In addition to its anti-malarial effect, it also has a potential broad-spectrum anti-viral effect. Hydroxychloroquine has showed the ability to inhibit SARS-CoV-2 in cell lines ($EC_{50} = 1.13 \mu\text{mol/L}$) in a previous study.^[21] Studies by Chinese scholars Shan Hong and Zhong Nanshan have provided evidence for the safety and effectiveness of hydroxychloroquine/chloroquine and showed that it can be used as a cost-effective treatment against the COVID-19.^[22] However, in a recent retrospective observational study, 96032 COVID-19 inpatients were recruited from 671 hospitals in 6 continents. The results of the study showed that hydroxychloroquine/chloroquine monotherapy or when combined with macrolides did not benefit the hospitalization of COVID-19, but increased the risk of in-hospital death and ventricular arrhythmia by 33% compared to the control group.^[23] Therefore, more evidence is needed to support its effectiveness and safety.

Convalescent plasma therapy (CPT) is passive immunotherapy that works to neutralize the antibodies against pathogens and is obtained from the plasma of recovery patients. This treatment strategy has been used in the treatment of outbreaks of infectious diseases such as influenza,^[24] measles, hemorrhagic fever in Argentina, Zika virus infection,^[25] MERS,^[26] and SARS. Research on plasma replacement antibodies containing highly potent anti-SARS-CoV-2, donated by recovered patients, has shown promising results, and these neutralizing antibodies have been used in the treatment of critically ill COVID-19 patients. However, there are certain limitations. For example, macromolecular proteins or cytokines in plasma may cause severe allergic reactions (hypotension, anaphylactic shock, etc.).^[27,28] The plasma that meets the requirements is limited and the quality requirement of the blood product is high. It is also necessary to ensure that the blood donors' antibody (IgG) concentration is sufficiently high. Although CPT has real and better efficacy, it still requires rigorous and larger-scale clinical trial verification.

TCM plays a huge role in the treatment of the COVID-19 virus.^[29] Lianhua Qingwen in TCM has been shown to successfully treat new coronary pneumonia and the mechanism of its action may be related to its broad-spectrum antiviral, antibacterial and antipyretic, cough and phlegm reduction, immune regulating, and other related properties.^[30] Some scholars believe that Lianhua Qingwen acts on the coronavirus through multiple components, multiple targets, and multiple pathways, and its main components have a good binding ability with Main Protease (Mpro) and Angiotensin-converting enzyme 2 (ACE2). Meta-analysis shows that Lianhua Qingwen when combined with Western medicine for the treatment of patients with COVID-19 shows efficacy and fewer adverse reactions.^[31] However, due to the limitations of the included literature, it is necessary to conduct further in-depth research using high-quality RCTs.

At present, the main prevention and control methods involved in the research include behavioral intervention, psychological intervention, environmental protection, and research. Effective behavioral intervention is currently the most important means to prevent and control the spread of new coronary pneumonia. Timely, orderly, efficient, and harmless disposal of medical waste and medical sewage and the prevention of secondary disasters in pandemic situations are the focus of the current research on the ecological environment.

Table 6

COVID-19 clinical trial vaccine research and development registration information table.

Types of vaccine	Preparation characteristics	Features	Country/Number	Intervention	Assign	Development progress Procedure	Size	Object	Phase	Main outcome indicators
Inactivated virus vaccine	Made after cultivation, proliferation, and inactivation by physical and chemical methods	<ul style="list-style-type: none"> Advantages: The virus particle structure is unchanged, the virus surface protein is retained, and the antigenicity is similar to the live virus; it will not replicate in the host; the classic research and development method, the technology is relatively mature and easy to prepare Disadvantages: Insufficient immunogenicity often requires multiple doses; some require adjuvants; protective effects vary widely; attention needs to be paid to antibody-dependent infection enhancement (ADE) (measles precedent) 	China/ChiCTR2000031809	Inactivated vaccine (Vero cells)	Randomized	1 dose	630	≥6 years old healthy people	I/II	Safety indexes of ADR [Time Frame: 0-7 days post-vaccination]
Adenovirus vector vaccine	Using harmless adenovirus as a carrier, carrying the S protein gene to stimulate the body to produce antibodies	<ul style="list-style-type: none"> Advantages: low toxicity of adenovirus, infection only causes mild cold symptoms; can induce cellular immunity and mucosal immunity; easy production and preparation without adjuvant; Ebola vaccine development experience Disadvantage: Neutralizing antibodies against common human serotype adenoviruses are common in the population, which will weaken the immune response induced by the corresponding adenovirus vector 	China/ChiCTR2000032459 China/CNCT04352608 China/NCT04313127	Inactivated vaccine (Vero cells) Inactivated vaccine (Vero cells) Adenovirus Type 5 Vector	Randomized Randomized Non-Randomized	1 dose 2 dose 1 dose	630 744 108	≥3 years old healthy people Healthy adults aged 18-59 years; Healthy people aged 18-60	I/II I/II I	Safety indexes of ADR [Time Frame: 0-7 days post-vaccination] Safety indexes of adverse reactions [Time Frame: From the beginning of the vaccination to 28 days after the whole schedule vaccination] Safety indexes of adverse reactions [Time Frame: 0-7 days post-vaccination]
Subunit vaccine	Genetic engineering to prepare viral S protein in vitro to stimulate human body to produce antibodies	<ul style="list-style-type: none"> Advantages: No viral genome, good safety, no disease caused by viral infection; can 	Canada/NCT04398147 China/NCT04341389 Australia/NCT04405908	Adenovirus Type 5 Vector Adenovirus Type 5 Vector SGB-2019: Adjuvant	Randomized Randomized Randomized	1 dose 1 dose 2 dose	696 508 150	18-84 year old healthy people 18-60 year old healthy people 18-75 year old healthy people	I/II II I	Incidence of Serious adverse events (SAE) in all groups [Time Frame: 6 months after the final vaccination] Occurrence of adverse reactions [Time Frame: 0-14 days post vaccination] Incidence of solicited adverse events (AEs) after vaccination [Time Frame: 7 days after the first or second vaccination.]

(continued)

Table 6
(Continued).

Types of vaccine	Preparation characteristics	Features	Country/Number	Intervention	Development progress		Object	Phase	Main outcome indicators
					Assign	Procedure			
Nucleic acid vaccine (DNA + mRNA)	Inject antigen (S protein) gene directly into human body, use human cells to produce S protein to stimulate human body to produce antibodies	<p>induce B cell and T cell dependent immune response</p> <ul style="list-style-type: none"> Disadvantages: often require multiple doses; may require adjuvant Advantages: the potential for a sustained immune response; mostly cause cellular immunity; SARS vaccine, MERS vaccine have completed clinical trials, have some experience Disadvantages: The effect of immune protection needs to be further studied; the drug delivery efficiency may not be high and the amount required is large; focus on safety 	America/NCT04336410	Drug:INO-4800; Device:CELLECTRA 2000	Non-Randomized	2 dose	≥18 years old healthy people	I	Percentage of Participants with Adverse Events (AEs) [Time Frame: Baseline up to Week 52]
			America/NCT04283461	mRNA-1273	Non-Randomized	2 dose	Healthy people aged 18-99	I	Frequency of solicited local reactogenicity adverse events (AEs) [Time Frame: Through 7 days post-vaccination]
			America/NCT04368728	BN1162b2	Randomized	2 dose	Healthy people aged 18-85	III	Percentage of participants reporting local reactions [Time Frame: For 7 days after dose 1 and dose 2]

4.4. Progress of vaccine research and development and follow-up clinical assumptions

Vaccines are the most effective means to prevent and control infectious diseases such as SARS-CoV-2,^[32] but their safety deserves attention. The WHO “COVID-19 Global Research Roadmap” points out that when animals immunized with the coronavirus vaccine are exposed to live virus again, antibody-dependent enhancement (ADE) effects may occur, increasing the disease severity post-vaccination.^[33] Selecting the appropriate target antigen and reducing the non-neutralizing antibody induction regions are the key measures to prevent ADE. At present, multiple research and development technologies are parallelly advancing vaccine development that includes inactivated vaccines, nucleic acid vaccines, recombinant viral vector vaccines, and subunit vaccines.^[34]

The inactivated vaccine is a classic traditional form of vaccine. It has previously induced the production of neutralizing antibodies in SARS-infected Rhesus monkeys. It has shown encouraging results in the initial phase I human clinical trials but has been stranded because phase II clinical trials have not yet been carried out.^[35] On January 24, 2020, the Chinese Center for Disease Control successfully isolated the first COVID-19 strain, which laid the foundation for the development of subsequent vaccines.^[36] Recombinant viral vector vaccines have been widely developed for SARS and MERS.^[37] Commonly used viral vectors include retroviral vectors, adenovirus vectors, and influenza virus vectors.^[38] At present, China has launched 1 adenovirus vector vaccine (Adenovirus Type 5 Vector, NCT04313127) and 2 lentivirus vector vaccines (NCT04299724, NCT04276896). Nucleic acid vaccines can be divided into mRNA vaccines and DNA vaccines. The first nucleic acid vaccine (mRNA-1273) for SARS-CoV-2 was developed by a US pharmaceutical company and a clinical trial (NCT04283461) was conducted at the National Institute of Allergy and Disease Transmission (NIAID).

At present, the COVID-19 vaccines that have entered clinical practice all over the world are in phase I or phase II. The phase 3 clinical trial (final phase) of the mRNA-1273 vaccine will start in July 2020, and will eventually enroll 30000 people. If a vaccine has been initially validated through phase I and II clinical trials (to ensure safety), a relatively large-scale single-arm (no control group, all vaccinated trial vaccine) phase III clinical design can be considered in an emergency. It will involve administering the vaccine first to medical staff, pandemic prevention personnel, and other susceptible people to provide the maximum possible protection. This can be followed by conducting a comparative analysis through the infection data of people in the unvaccinated area and finally determining the actual results of the phase III clinical trial. Eyal et al^[39] believe that some subjects can be selected, vaccinated, and then challenged by a virus challenge (voluntarily) to accelerate the progress of phase III clinical research of the COVID-19 vaccine.

In conclusion, there were issues of unclear classification of research types and irregular registration behavior. Within the studies researched, heterogeneity existed for various parameters. Differences in the types of studies, intervention, and registration sources of the studies led to significant differences in certain parameters of the COVID-19 clinical trials. The statistics of high-frequency drugs and the progress of vaccines may provide an informative reference for the prevention and control of COVID-19.

5. The advantages and disadvantages of this study

1. This review describes for the first time the results of the 2019 Coronary Virus Disease (COVID-19) clinical trial, the difference between the results measurement tool and the results measurement time report.
2. Search all the databases of the clinical trial registration platform accepted by the international clinical trial registration platform, and consider randomized controlled trials and observational studies.
3. The purpose of this review is to provide a list of the results of the COVID-19 clinical trial, which takes into account vaccine interventions.
4. This study provides an information-based data foundation and information reference for curbing the spread of the COVID-19 pandemic.

6. Conclusion

Amongst the studies researched, heterogeneity existed for various parameters. Differences in the type of study, interventions, and registration sources of the studies led to significant differences in certain parameters of the COVID-19 clinical trials. The statistics of high-frequency drugs and the progress of vaccine trials may provide an informative reference for the prevention and control of COVID-19.

Author contributions

Conceptualization: Gao Song, Mengqun Cheng.
Data curation: Gao Song, Mengqun Cheng.
Formal analysis: Gao Song, Mengqun Cheng.
Funding acquisition: Gao Song.
Investigation: Gao Song, Mengqun Cheng.
Methodology: Gao Song.
Project administration: Gao Song, Xianwen Wei.
Resources: Xianwen Wei.
Software: Xianwen Wei.
Supervision: Xianwen Wei.
Writing – original draft: Gao Song.
Writing – review & editing: Gao Song.

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