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Clinical Trials on COVID-19: What is Being Researched in the United States?

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Abstract

The emergence of Coronavirus Disease 2019 (COVID-19) in late 2019 has brought great challenges to public health worldwide and, to date, there is no specific approved therapeutic protocol. Therefore, this chapter will analyze types of intervention for use in patients with COVID-19 developed by American researchers from records made on the Clinical Trials platform. For the search strategy, keywords “COVID-19” in the “Condition or Disease” section and “United States” in the “Country” section were used. No filters were applied. Data were descriptively analyzed. In total, 1,182 studies were obtained, of which 496 met the eligibility criteria. Sample size ranged from 1 to 10,000 participants. Most studies involved the age group of 18–64 years (48.6%). As for design, randomized type (80.5%), parallel (75.6%), open designs (38.7%) and those with therapeutic purpose (88.3%) were more frequent. Most clinical trials used the two-arm trial (67.3%), researched drugs (64.8%), used placebo (55.2%) and were sponsored by pharmaceutical/biotechnology companies (35.4%). Clinical trials developed by American researchers on COVID-19 involve adult and elderly participants, with predominance of randomized, parallel and open design, for therapeutic purposes and mostly evaluated immunosuppressants or combinations of antivirals/immunosuppressants. The drugs and biological products Remdesivir, Baricitinib in combination with Remdesivir, Bamlanivimab and Etesevimab, REGEN-COV and COVID-19 convalescent plasma were also used, authorized for emergency use.

Keywords: Clinical Trial, Evidence-Based Practice, Pharmaceutical Preparations, Vaccines, COVID-19, Coronavirus Infection

1. Introduction

In March 2020, the World Health Organization (WHO) recognized Coronavirus Disease 2019 (COVID-19) as a public health problem and declared the state of pandemic contamination [1]. Since its detection in late 2019, in China, the newly discovered virus, called SARS-CoV-2 [2] spread rapidly around the world with cases, to date, in 223 countries, with more than 127 million infected individuals and nearly 3 million deaths [3]. The region of Americas concentrates almost half of all diagnosed individuals, with the United States being the most affected country, totaling 30 million cases [3].

SARS-CoV-2 belongs to a family of single-stranded, positive-sense and enveloped RNA viruses, known as *Coronaviridae* [4], has high mutation rate and rapid spread, with multiple mutations having appeared and spread during the pandemic [5, 6]. The transmission of the virus occurs through droplets expelled by a person with the disease or through contact with contaminated surfaces [7].

In general, patients with COVID-19 have fever, cough, myalgia, nausea, diarrhea, reduced smell and taste, as well as mild breathlessness [8]. In the most severe cases, patients can develop Acute Respiratory Distress Syndrome (ARDS), heart failure, shock and renal failure [9]. Elderly, obese and individuals with pre-existing conditions, such as diabetes, hypertension, cardiovascular and pulmonary diseases, cancer, chronic kidney disease, among others, have higher risk of progressing to more critical cases of the disease [10]. In addition to symptoms and severity of the disease, the impact of COVID-19 affects all aspects of our lives, generating financial consequences, insecurity and anxiety [11].

Advances have been made in the knowledge of COVID-19 and in the development of safe and effective vaccines [12]. However, there is still no specific pharmacological protocol approved to prevent and/or reduce contamination by the virus, so that there are countless ongoing researches to find an appropriate treatment [13]. The development of vaccines, convalescent plasma therapies, cell-based and monoclonal antibody therapies are some of the treatments studied worldwide. However, the development of new drugs is a long and expensive process, and the current health emergency has led to the use of existing drugs [14].

The pandemic has induced the global scientific community to focus efforts on COVID-19 [15] and clinical trials represent the gold standard for evidence-based practice [16], as they are important methods for assessing intervention modalities, generating impact on current and future clinical practice [17]. However, attention should be paid to clinical trials with inadequate or low-quality designs, and it is important to analyze their designs on clinical trial registration platforms to identify those that provide the best scientific evidence that can reduce the effects of the COVID-19 pandemic [18].

In view of the fact that SARS-CoV-2 is a virus with characteristics never before studied, with several consequences that go beyond contamination, and in the absence of an approved effective therapy, correctly designed clinical trials are essential for evaluating interventions in order to prevent and contain the spread of the disease. Thus, the guiding issue that supported this chapter was: “Which interventions for use in patients with COVID-19 are being evaluated by American researchers?”

2. Methods

The database chosen for this study was the Clinical Trials platform (<https://clinicaltrials.gov/>), which comprises a web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions [19]. In the search strategy, keywords “COVID-19” in the “Condition or Disease” section and “United States” in the “Country” section were used.

No filters were applied, so that all registered clinical trials were analyzed. Data were collected in March 2021 by a single previously trained researcher. Studies with suspended, withdrawn and terminated recruitment status, observational and expanded access studies, and those that did not mention COVID-19 diagnosis and those including healthy patients among their eligibility criteria were excluded.

The following information was collected: study location, number of participants, age groups of subjects (0–17, 18–64, >65), allocation (randomized, non-randomized e n/a), intervention model (single group assignment, sequential assignment,

crossover assignment, parallel assignment and factorial assignment), masking (blind, double-blind, triple-blind, quadruple-blind and open label), purpose (diagnostic, treatment, prevention, basic science, supportive care, health services research, device feasibility, screening and other), diagnostic criteria for COVID-19 (confirmed, suspect and confirmed or suspect), other eligibility criteria, recruitment status (completed, recruiting, active, not recruiting, not yet recruiting and enrolling by invitation), numbers of arms, type of intervention (dietary supplement, drug, biological, device, diagnostic test, procedure, radiation, behavioral, combination product and other), phase (early phase 1, phase 1, phase 2, phase 3, phase 4, phase 1 and phase 2, phase 2 and phase 3 and n/a), presence of placebo (yes and no), comparison arm (yes and no), and sponsor (university, pharmaceutical/biotechnology company, research organizations, hospital, health care provider, doctor, united states department of defense and philanthropy).

Types of intervention were classified according to the WHO's Anatomical Therapeutic Chemical Classification System [20]. In cases where they are not included in the WHO's ATC, information present on the companies' websites was used.

Data were tabulated and analyzed using the Microsoft Excel 2016 for Windows software (Microsoft Press, Redmond, WA, USA) and descriptively presented.

3. Results

In total, 5,129 records involving COVID-19 were found and, after the search strategy, 1,182 (23%) corresponded to clinical trials developed in the United States. Of these, eight studies that were suspended, 22 that had been withdrawn, 25 terminated, 325 observational studies, 18 expanded access, 37 that did not include COVID-19 diagnosis and, finally, 251 clinical trials using healthy patients were excluded. At the end, 496 studies met the eligibility criteria and were selected.

The geographic distribution of studies highlights the state of California as the main place for carrying out these surveys (155 studies), followed by Florida (124 studies), Texas (121 studies), Nova York (115 studies), Illionois (86 studies), Massachusetts (81 studies), Pennsylvania (78 studies), North Carolina (75 studies), Washington and Ohio (73 studies each), Michigan (71 studies), Maryland (70 studies), Georgia (66 studies), Louisiana (64 studies), New Jersey (56 studies), Virginia and Arizona (50 studies each), Minnesota (45 studies), Colorado (39 studies), Alabama (38 studies), Tennessee (35 studies), Missouri (33 studies), Connecticut (30 studies), Utah (29 studies), Oregon (28 studies), South Carolina and Kansas (27 studies), Kentucky (25 studies), New Mexico and Nebraska (22 studies each), Indiana and Iowa (21 studies), Wisconsin and Mississippi (20 studies each), Arkansas (16 studies), Idaho and Rhode Island (14 studies), Oklahoma (11 studies), West Virginia (10 studies), Maine and South Dakota (9 studies each), Hawaii and Montana (7 studies each), Vermont (3 studies), and Alaska and Delaware (1 studies each).

The number of participants ranged from 1 to 10,000 individuals. Most clinical trials analyzed involved adults and older adults, with higher percentage in the age group of 18–64 years (48.6%), while surveys that recruited children and adolescents represented only 2.9%.

Regarding the allocation of participants, only 26 studies (5.2%) were not characterized as randomized. The most frequent intervention model is the parallel (75.6%). Regarding the type of masking, the open study model (38.7%) is the most prevalent, followed by the double-blind model (21.4%), while single-blind studies corresponded to only 4.4%. Studies with therapeutic purposes were carried out in the majority (88.3%) and there is predominance of those who consider proven and positive COVID-19 diagnosis (89.1%) as an inclusion criterion (**Table 1**).

Variables	n	%
Age Groups (in years)*		
0–17	29	2.9
18–64	489	48.6
> 65	487	48.5
Allocation		
Randomized	399	80.5
Non-Randomized	26	5.2
N/a	71	14.3
Intervention Model		
Single Group Assignment	86	17.3
Sequential Assignment	26	5.2
Crossover Assignment	3	0.6
Parallel Assignment	375	75.6
Factorial Assignment	3	1.2
Masking		
Blind	22	4.4
Double-blind	106	21.4
Triple-blind	73	14.7
Quadruple-blind	103	20.8
Open Label	192	38.7
Purpose		
Diagnostic	15	3.0
Treatment	438	88.3
Prevention	12	2.4
Basic Science	2	0.4
Supportive Care	17	3.4
Health Services Research	2	0.4
Device Feasibility	2	0.4
Screening	1	0.2
Other	7	1.4
Diagnostic Criteria for COVID-19		
Confirmed	442	89.1
Suspect	11	2.2
Confirmed or suspect	43	8.7
Recruitment Status		
Completed	66	13.3
Recruiting	295	59.5
Active, not recruiting	68	13.7
Not yet recruiting	50	10.1
Enrolling by invitation	17	3.4

Variables	n	%
Numbers of Arms		
1	70	14.1
2	334	67.3
3	43	8.7
4	26	5.2
5	7	1.4
6	8	1.6
8	4	0.8
10	1	0.2
12	2	0.4
No information	1	0.2
Type of Intervention*		
Dietary Supplement	16	3.1
Drug	335	64.8
Biological	80	15.5
Device	35	6.7
Diagnostic Test	8	1.5
Procedure	4	0.8
Radiation	4	0.8
Behavioral	4	0.8
Combination Product	3	0.6
Other	28	5.4
Phase		
Early Phase 1	12	2.4
1	45	9.1
2	214	43.2
3	71	14.3
4	26	5.2
1 e 2	35	7.1
2 e 3	26	5.2
N/a	67	13.5
Presence of Placebo		
Yes	274	55.2
No	221	44.6
No information	1	0.2
Comparison Arm		
Yes	121	54.5
No	100	45.0
No information	1	0.5

Variables	n	%
Sponsor*		
University	201	29.4
Pharmaceutical / Biotechnology Company	242	35.4
Research Organizations	65	9.5
Hospital	82	12.0
Health Care Provider	39	5.7
Doctors	36	5.2
United States Department of Defense	6	0.9
Philanthropy	13	1.9

*Some studies involved more than one age group, type of intervention and sponsor; N/a = Not applicable.

Table 1.
Characteristics of the sample and study design of clinical trials.

Other eligibility criteria used by researchers were the inclusion of individuals with associated risk factors (28 studies), including cancer (4 studies), type 1 or type 2 diabetes mellitus (3 studies) and heart diseases (1 study).

Regarding recruitment status, at the time of data collection, 59.5% of clinical trials were recruiting participants and 13.7% were active, but not recruiting. Regarding the number of arms, most studies use the two-arm test (67.3%). Most clinical trials research a new drug (64.8%), are in phase 2 (43.2%), 55.2% use placebo and 54.5% use comparison arm. As for sponsors, pharmaceutical/biotechnology companies (35.4%) and universities (29.4%) are those that most invest in clinical trials (**Table 1**).

Regarding the identification and classification of drugs, biological interventions, dietary supplements, combined products and some other interventions, 434 clinical trials use interventions in monotherapy and 67 make use of combinations. In monotherapy, most trials assess immunosuppressants (49 studies), followed by COVID-19 Convalescent Plasma (40 studies), antivirals (32 studies), anticancer (30 studies), antithrombotic (24 studies), anti-inflammatory agents (16 studies), antifibrinolytics (14 studies), antimalarials (13 studies), immunostimulants (7 studies), expectorants (6 studies), antibacterials (5 studies), antiparasitic and corticosteroids (4 studies each), antidepressants (3 studies), sex hormones and modulators of the genital system (2 studies) and antiprotozoals (1 study) (**Tables 2 and 4**). Clinical trials using combinations use antivirals /immunosuppressants (9 studies), antimalarials /antibiotics (6 studies), antithrombotic agents (4 studies) and antivirals/corticosteroids (**Tables 3 and 4**).

Interventions and Classes	n*	Interventions and Classes	n*	Interventions and Classes	n*
Antithrombotic Agents	24	Interferon	4	AZD7442	2
Heparin	6	CPI-006	2	COVID-19 Therapeutic Biologics - Spike-GM-CSF Protein Lactated Ringer's Injection	2
Enoxaparin	4	Sargramostim	1	Zinc	2
Apixaban	3	Anticancer	30	IVIG	2
Defibrotide	2	Colchicine	5	Octagam	2
Rivaroxaban	2	Ibrutinib	3	GAMUNEX-C	1

Interventions and Classes	n [*]	Interventions and Classes	n [*]	Interventions and Classes	n [*]
Dipyridamole	2	CYT107	2	Garadacimab	1
Tenecteplase	2	Duvelisib	2	Sodium bicarbonate	1
Acetylsalicylic Acid	1	Ruxolitinib	1	NasoVAX	1
VentaProst	1	Abivertinib	1	NA-831	1
TM5614	1	Pacritinib	1	Ifenprodil	1
Antifibrinolytics	14	Decitabine	1	ABBV-2B04	1
Camostat	9	Bempegaldesleukin	1	ABBV-47D11	1
Tranexamic acid	2	Etoposide	1	Ibudilast	1
Ulinastatin	1	Bicalutamide	1	MAS825	1
LYT-100	1	Imatinib	1	BGB-DXP593	1
BLD-2660	1	Upamostat	1	PUL-042	1
Antimalarials	13	Nintedanib	1	PurCo	1
Chloroquine or hydroxychloroquine	11	Acalabrutinib	1	Bucillamine	1
Tafenoquine	1	Degarelix	1	Pioglitazone	1
Artesunate	1	Antroquinonol	1	Gimsilumab	1
Antivirals	24	Selinexor	1	BI 764198	1
Molnupiravir	4	Zanubrutinib	1	Zilucoplan	1
Favipiravir	3	FT516	1	Lanadelumab	1
Lopinavir/Ritonavir	2	CYNK-001	1	rNAPc2	1
Brequinar	2	Antiparasitic	4	Aprepitant	1
Silmitasertib	2	Ivermectin	2	Brexanolone	1
Apilimod Dimesylate	1	Niclosamide	1	Pepto Bismol	1
Maraviroc	1	Disulfiram	1	Ruconest	1
Liquid Alpha1-Proteinase Inhibitor	1	Antiprotozoals	1	Isavuconazonium	1
RBT-9	1	Atovaquone	1	Fostamatinib	1
AT-527	1	Corticosteroids	4	VIB7734	1
BTL-TML-COVID	1	Dexamethasone	2	Pamrevlumab	1
LAU-7b	1	Ciclesonide	1	CAP-1002	1
Veru-111	1	Prednisone	1	Linagliptin	1
PTC299	1	Anti-inflammatory	16	CM4620-IE	1
PF-07304814	1	Acebilustat	2	Vadadustat	1
RTB101	1	Ampion	2	Zofin	1
Antibacterials	5	N-acetyl glucosamine	1	ADG20	1
Azithromycin	2	Alvelestat	1	GC4419	1
Doxycycline	1	Dociparstat	1	Essential Oil Blend	1
Brilacidin	1	Ensifentrine	1	Fenofibrate	1
Carrimycin	1	Bardoxolone Methyl	1	ATI-450	1
Antidepressants	3	Indomethacin	1	Xuanfei Baidu Granules	1
Fluvoxamine	2	EDP1815	1	Emricasan	1

Interventions and Classes	n [*]	Interventions and Classes	n [*]	Interventions and Classes	n [*]
Fluoxetine	1	LSALT peptide	1	ORTD-1	1
Immunosuppressants	49	OP-101	1	Metformin	1
Tocilizumab	7	FSD201	1	Umbilical Cord Lining Stem Cells	1
Anakinra	3	RLS-0071	1	BGE-175	1
Cyclosporine	2	ST266	1	Chlorine dioxide	1
Sirolimus	2	Sex hormones and modulators of the genital system	2	Prazosin	1
Ravulizumab	2	Estradiol	1	Cetylpyridinium Chloride	1
Sarilumab	2	Progesterone	1	Peroxil	1
Leflunomide	2	Expectorants (mucolytics)	6	Colgate Total Zero	1
Razuprotafib	1	N-acetylcysteine	3	Saline rinse	1
Dapansutride	1	Pulmozyme	2	Crizanlizumab	1
Abatacept	1	Dornase Alfa	1	AT-001	1
Losmapimod	1	Outras	187	Hyperpolarized Xe129	1
Apremilast	1	Renin-angiotensin system inhibitors	11	Atorvastatin	1
Olokizumab	1	Mesenchymal stem cells (MSCs)	11	Glycine	1
Infliximab	1	Nitric Oxide	7	Alanine	1
Tociliuzumab	1	Cytotoxic T Lymphocytes	7	Thymalfasin	1
Canakinumab	1	Bamlanivimab	6	TB006	1
Sirukumab	1	Clazakizumab	6	PF-06650833	1
Lenzilumab	1	Chlorhexidine	5	Angiotensin	1
Otilimab	1	Vitamin D	4	Tradipitant	1
Tofacitinib	1	Vitamin C	4	Resistant starch	1
Auxora	1	Mavrilimumab	4	F-652	1
APL-9	1	Povidone Iodine	4	Omega-3	1
CD24Fc	1	Fisetin	3	L-Citrulline	1
TL-895	1	Leronlimab	3	FoTv	1
TD-0903	1	Listerine	3	VisAcT	1
EB05	1	Hydrogen Peroxide	3	Regadenoson	1
ATYR1923	1	Famotidine	2	Sulfur hexafluoride lipid-type A	1
CERC-002	1	Melatonin	2	Lucinactant	1
M5049	1	VIR-7831	2	CBDRA60	1
BMS-986253	1	Nitrogen gas	2	SBI-101	1
GLS-1027	1	NT-I7	2	Zavegepant	1
UTTR1147	1	Betadine	2	Neuromuscular Blocking Agents	1
MSTT1041A	1	Naltrexone	2	<i>Artemesia annua</i>	1
TJ003234	1	Human Amniotic Fluid	2	<i>Nerium oleander</i>	1

Interventions and Classes	n [*]	Interventions and Classes	n [*]	Interventions and Classes	n [*]
Immunostimulants	7	KB109	2		

**Some studies used several interventions.
The bold entries refer to the drug classes and the total interventions of each class of drugs and biological products according to the WHO's Anatomical Therapeutic Chemical Classification System or information present on the companies' websites.*

Table 2.
Monotherapy interventions used in experimental groups of registered clinical trials on COVID-19.

Interventions and Classes	n [*]
Antithrombotic Agents Combinations	4
Heparin + P2Y12	2
Dipyridamole + Acetylsalicylic Acid	1
Enoxaparin + Heparin + Fondapariniux + Argatroban	1
Antimalarials + Antibiotics	6
Hydroxychloroquine + Azithromycin	6
Antivirals + Immunosuppressants	7
Remdesivir + Tocilizumab	1
Remdesivir + Infliximab	1
Remdesivir + Apremilast	1
Remdesivir + Abatacept	1
Remdesivir + Risankizumab	1
Remdesivir + Apremilast	1
Remdesivir + Lenzilumab	1
Antivirals + Corticosteroids	2
Atazanavir + Dexamethasone	1
Remdesivir + Dexamethasone	1
Other Combinations	41
Remdesivir + Cenicriviroc	2
Valproate + Quetiapine	1
PurInf (I) + PurInf (II) + PurInf (III)	1
PurPhl + PurClo	1
Colchicine + Rosuvastatin	1
Colchicine + Naltrexone	1
Naltrexone + Ketamine	1
BRII-196 + BRII-198	1
NA-831 + Dexamethasone	1
NA-831 + Atazanavir	1
IVIG + Remdesivir	1
Rintatolimod +Interferon	1
Remdesivir + Interferon	1
Remdesivir + Icatibant	1
Remdesivir + Razuprotafib	1
Remdesivir + anti-CD14	1

Interventions and Classes	n*
Plasma + Ruxolitinib	1
Bamlanivimab + VIR-7831	1
ABBV-47D11 + ABBV-2B04	1
Mesenchymal Stem Cells + Heparin	1
Metformin + Naltrexone	1
Resveratrol + Vitamin D	1
Nitazoxanide + Vitamin Super B-Complex	1
Vitamin C + Zinc	1
Resveratrol + Zinc	1
Famotidine + N-Acetyl cysteine	1
Chlorine dioxide + Zinc acetate	1
Atovaquone + Azithromycin	1
Camostat Mesilat + Bicalutamide	1
Xylitol + Grapefruit Seed Extract	1
Peroxil + Chlorhexidine	1
Hydroxychloroquine + Azithromycin + Zinc	1
Hydroxychloroquine + Zinc + Doxycycline	1
Hydroxychloroquine + Nitazoxanide + Ribavirin	1
Hydroxychloroquine + Azithromycin + Ritonavir + Lopinavir	1
Bamlanivimab + Remdesivir + VIR-7831 + BRII-196/BRII-198 + AZD7442	1
Chlorine dioxide + Famotidine + Lactoferrin + green tea extract	1
Chlorine dioxide + Zinc acetate + Famotidine + Lactoferrin + green tea extract	1
Hydroxychloroquine + Azithromycin + Vitamin C + Vitamin D + Zinc	1
Ivermectin + Doxycycline Hc + Vitamin C + Vitamin D + Zinc	1

*Some studies used several interventions.

Table 3.
Combinations of interventions used in experimental groups of registered clinical trials on COVID-19.

Interventions and Classes	n*
COVID-19 Convalescent Plasma	40
Antivirals	8
Remdesivir	8
Antivirals + Immunosuppressants	2
Remdesivir + Baricitinib	2
Other Combinations	5
Bamlanivimab + Etesevimab	2
REGN10933 + REGN10987	3

*Some studies used several interventions.
The bold entries refer to the drug classes and the total interventions of each class of drugs and biological products according to the WHO's Anatomical Therapeutic Chemical Classification System or information present on the companies' websites.

Table 4.
Monotherapy and combinations of interventions with Emergency Use Authorizations (EUA) issued by U.S. Food and Drug Administration (FDA) used in experimental groups of registered clinical trials on COVID-19.

4. Discussion

Many clinical trials related to the COVID-19 pandemic have emerged in response to society's concerns related to the impacts of the pandemic, and in response to this global emergency. Scientific production on the topic is dynamic and fast, which makes the sharing and synthesis of knowledge important [15]. In this context, the characterization of research efforts can help professionals, researchers, and managers to understand the relevant aspects of the disease.

Considering the serious public health crisis of COVID-19 and the search for discovering safe and effective treatments, high-quality research is needed to evaluate interventions for the prevention of the disease and its treatment. Clinical trials properly designed and conducted make their results valid and can significantly contribute to the effort to improve the effectiveness and efficiency of health interventions [21].

"Clinical Trials" is a robust platform for registering clinical trials, containing detailed information on a large amount of clinical research conducted in 219 countries [22]. According to the Dimensions database, "Clinical Trials" is the leading platform for registering clinical trials on COVID-19, accounting for 58.8% of all registrations [23]. Of the clinical trials registered and found on this platform, a significant number is being developed by American researchers. This research leadership is underpinned by huge public funding, mainly from the National Institutes of Health (NIH), which has already received more than US\$ 3.6 billion to fund research on COVID-19 [24], as well as from government agencies, universities and the private sector [25], which demonstrates the urgency of the USA in the face of the severity with which the disease reached the country [18].

Among studies analyzed, the majority of participants are adults and older adults. It is known that COVID-19 is less prevalent in children compared to adults and adolescents and that younger individuals infected with SARS-CoV-2 have less severe symptoms and lower hospitalization and lethality rates [26, 27]. In March 31, 2021, 11.7% of COVID-19 cases in the United States were of children and adolescents up to 17 years of age, corresponding to almost 3 million cases. Of these, for the age group of 0–4 years, there were only 104 deaths (<0.01%) and, for the age group of 5–17 years, only 228 deaths (0.1%) [27]. Therefore, these may be the reasons for choosing the age group of adults and older adults.

The most frequent study design was randomized allocation, the parallel intervention model and the open masking type. The randomization of a clinical trial ensures that, in addition to intervention, there are no systematic differences between study groups, providing impartial results regarding the effect of interventions and reducing biases [18, 28]. Even so, only randomization does not exclude the possibility of systematic differences, because since those involved in a clinical trial are aware of the attributions of interventions, which can influence the result and introduce bias [29]. In our study, masking was not feasible mainly for ethical reasons or because patients are incorporated into healthcare environments, making it difficult to blind the team that manages patient care [30].

There were greater number of clinical trials for therapeutic purposes that evaluate some drug as a type of intervention. These results may be related to the current world scenario and the urgent need for studies analyzing which treatments are shown to be most effective against COVID-19 [18] in an adequate and quick manner. The discovery of an efficient therapy would allow the prophylaxis of health professionals who are on front lines, so that they could get back to work more quickly, in addition to reducing the time spent by critically ill patients in intensive care units, freeing beds [31] and reducing mortality rates. Many studies using a placebo group were also found, and due to the lack of approved available treatment, this procedure is ethically acceptable [18].

In this study, the most frequent sponsors were pharmaceutical/biotechnology companies and universities. However, in the evaluated clinical trials, there was the collaboration of several companies, academic institutions, government agencies, non-profit organizations and individual medical researchers to properly implement resources in the fight against COVID-19 in order to concentrate and accelerate the development and implementation of therapies. This partnership of efforts may reflect the so-called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), conducted by NIH and announced in April 2020, in which researchers continue to work intensively to develop new and better treatments [32].

Regarding the classification of many tested drugs, biological interventions, dietary supplements, combined products and some other types of intervention, heterogeneity of classes used can be observed. Most clinical trials have been evaluated immunosuppressants or combinations of antivirals/immunosuppressants, some already with USA issued by the FDA and redirected for the treatment of COVID-19, such as the combination of immunosuppressant Baricitinib – used to treat rheumatological diseases [33] – with antiviral Remdesivir – used to treat patients infected with the Ebola virus, MERS-CoV and SARS-CoV-1 [34], and its use as monotherapy for certain patients hospitalized with COVID-19.

Other authorized drugs that deserve mention are the biological products Bamlanivimab and Etesevimab – neutralizing IgG1 monoclonal antibodies that bind to different but overlapping epitopes in the binding domain to the SARS-CoV-2 spike protein [35] –, REGEN-COV (Casirivimab and Imdevimab) – neutralizing recombinant human IgG1 monoclonal antibodies that target the binding domain to the SARS-CoV-2 spike protein receptor [36] –, and the COVID-19 convalescent plasma – collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies [37].

The COVID-19 pathogenesis begins with the replication of SARS-CoV-2, subsequently followed by an exaggerated immune /inflammatory response to the virus that leads to tissue damage. Regarding this knowledge, it is assumed that antiviral therapies would have greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies may be more beneficial in later stages of COVID-19 [33]. The use of these existing drugs helps reducing the cost and time of research; however, further large-scale studies must be carried out to assess the benefits and safety of these drugs.

The findings reported here make it clear that researchers from different fields of medicine have worked together in the development and clinical evaluation of several drugs aimed at treating the numerous medical complications caused by COVID-19. Extensive financial resources, made available by universities and pharmaceutical and biotechnology companies, have been applied in order to allow the conduction of clinical trials with high methodological and scientific rigor for both diagnostic and treatment purposes. Undeniably, the emergency approval of the tested drugs described here by the FDA, while making it possible to save thousands of lives in the American territory, has allowed a better understanding of their effects on individuals affected by COVID-19, which knowledge has been shared and put into practice by managers and medical teams from various countries around the world.

Therefore, during the COVID-19 pandemic and due to all resulting restrictions and difficult circumstances, good scientific practice and data transparency are essential principles that should guide the conduction of clinical trials. The sharing of these results, when properly carried out, helps professionals to make decisions, as well as researchers to identify gaps and more promising interventions, to avoid research waste and to expose patients to unnecessary risks, consequently contributing to the advancement of scientific knowledge.

5. Conclusion

Clinical trials developed by American researchers involving COVID-19 include adult and elderly participants, with predominance of randomized, parallel and open design, those for therapeutic purposes and those that mostly evaluate immunosuppressants or combinations of antivirals/immunosuppressants. The drugs and biological products Remdesivir, Baricitinib in combination with Remdesivir, Bamlanivimab and Etesevimab, REGEN-COV and COVID-19 convalescent plasma were also used, authorized for emergency use.

Conflict of interest


The authors report no conflicts of interest.

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