

Systematic Review

A systemic review of clinical trials of COVID-19, registered in WHO-ICTRP

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ABSTRACT

In September 2004, International Commission of Medical Journal Editors implemented a dramatic and important policy for the condition of publication of clinical trials. The condition was that clinical trials must be registered in a public trial registry. World Health Organization-International Clinical Trials Registry Platform (WHO-ICTRP) is the globally centralised network composed of primary registries and partner registries along with data providers. COVID-19 is a pandemic and a significant social and economical health burden. In this event numbers of trials have been undertaken by the medical professionals and research workers in every part of the world. Here we have analysed registered clinical trials for the detection, treatment and prevention of COVID-19 to provide a summary of global response w.s.r.to WHO-ICTRP. The objective of this study was to collect the data of registered clinical trials for the therapeutic and preventive measures for COVID-19 which are registered in WHO-ICTRP and analyse global response of COVID-19. WHO-ICTRP database has 20 fields of mapping. Out of these, we have analysed 6 fields of this registry, for this study purpose: public title, scientific title, study type, countries, intervention and primary outcome. Clinical trials are focused on chloroquine, hydroxychloroquine, lopinavir ritonavir combination, Remdesivir, Favipiravir, Tocilizumab and Interferon. Also, it is seen that convalescent plasma therapy is a promising intervention. Observational trials are directed mainly on the clinical features and distinguish COVID-19 from other influenza like illnesses.

Keywords: COVID-19, Registered clinical trial, ICTRP, Interventional trial, Observational trial

INTRODUCTION

In September 2004, International Commission of Medical Journal Editors (ICMJE) implemented a dramatic and important policy for the condition of publication of clinical trials.^{1,2} the condition was that clinical trials must be registered in a public trial registry.³ Subsequently every region, country and regulatory authorities around the world prepared their publicly accessible registry and began posting of clinical trial information in their respective registry.

Clinical trial registry of India (CTRI) under the watchful eyes of ICMR is the primary registry of India. It is expected that every clinical trial originating in India must get registered in CTRI.⁴ World Health Organization-International Clinical Trials Registry Platform (WHO-ICTRP) is the globally centralised network composed of primary registries and partner registries along with data providers.

COVID-19 is a pandemic and a significant social and economical health burden.

Global response for COVID-19 is unprecedented. Medical fraternity is in the search of treatment i.e. management and/or effective preventive therapeutic approach. In this event numbers of trials have been undertaken by the medical professionals and research workers in every part of the world.

Every clinical trial should be registered to improve the awareness of similar trials so that researcher can avoid unnecessary duplication. It improves quality of clinical trial by making it possible to identify problems early in the research design. It helps to make informed decisions by eliminating publication bias and selective reporting. Registering clinical trial and describing progress of clinical trial makes researchers and potential participant to be aware of recruitment in ongoing clinical trial.

Health care professionals may have interest in clinical trials. It also can help them to make prospective meta analysis of the clinical trials. Here we have analysed registered clinical trials for the detection, treatment and prevention of COVID-19 to provide a summary of global response with special reference to WHO-ICTRP.⁵

Objectives

The objective of this study was to collect the data of registered clinical trials for the therapeutic and preventive measures for COVID-19 which are registered in WHO-ICTRP and analyse global response of COVID-19 (1135 clinical trials were registered in ICTRP database and we downloaded this database on 21st April 2020 with last refreshed on 14th April 2020).⁵

METHODS

WHO designated COVID-19 a "public health emergency of international concern" on 30 January 2020 and declared it a pandemic on 11 March 2020.

WHO-ICTRP database is regularly updated on every Tuesday and Friday of the week. 1135 clinical trials were registered in ICTRP database and we downloaded this database on 21st April 2020 with last refreshed on 14th April 2020.

WHO-ICTRP database has 20 fields of mapping. With the help of public title, scientific title, study type, countries, intervention and primary outcome we analysed the data for global response of COVID-19 in respect of therapeutic and preventive measures.

Registry search strategy

1135 clinical trials were registered in ICTRP database and we downloaded this database on 21st April 2020 with last refreshed on 14th April 2020. Out of very

precise, precise, very sensitive, sensitive key word search strategy, we adopted just one term for the single trial.^{6,7}

For study type, a simple keyword search from the study type field reveals us different 11 types of clinical trial.

For country, a simple search from country field reveals the countries where the clinical trials have been primarily registered (e.g. for India, CTRI is the primary register).

From retrieved data it is evident that globally research scientists are using available drug molecules for the successful treatment/prevention of COVID-19 pandemic. As we know that SARS-CoV-2 is a single stranded RNA virus which encodes for four glycoprotein's essential for viral life cycle. Hence anti-viral, antibiotics, immunosuppressant, and monoclonal antibodies are the promising medicines for the global clinical trial research work.⁸

Hence for interventions we performed a keyword search for the single molecule in the field of public title, scientific title and intervention and fetched data from this database. With the help of Boolean search, many clinical trials intervene with two or more than two drug molecule e.g. chloroquine and lopinavir/ritonavir, lopinavir/ritonavir and interferon β -1a.

Inclusion criteria

Clinical trials enlisted in WHO-ICTRP retrieved on 21st April 2020 which was last refreshed on 14th April 2020. Total number of trials enlisted in WHO-ICTRP is 1135.⁵

Exclusion criteria

Surgical interventions

Other registry platforms clinical trials e.g. CTRI, Cochrane Central Register of Controlled Trials (CENTRAL).^{5,9}

All other clinical trials from ICTRP database which are not on COVID-19.

RESULTS

Number of trials- study type wise

The number of trials were interventional trials (study type) 654 included interventional clinical trials, 5 expanded access trials, 3 treatment trials, observational (study type) included 406 observational clinical trials, 10 epidemiological studies, 7 health service research, 7 basic science study, 3 prevention studies, 2 prognostic studies, 1 screening and 37 diagnostic (study type).

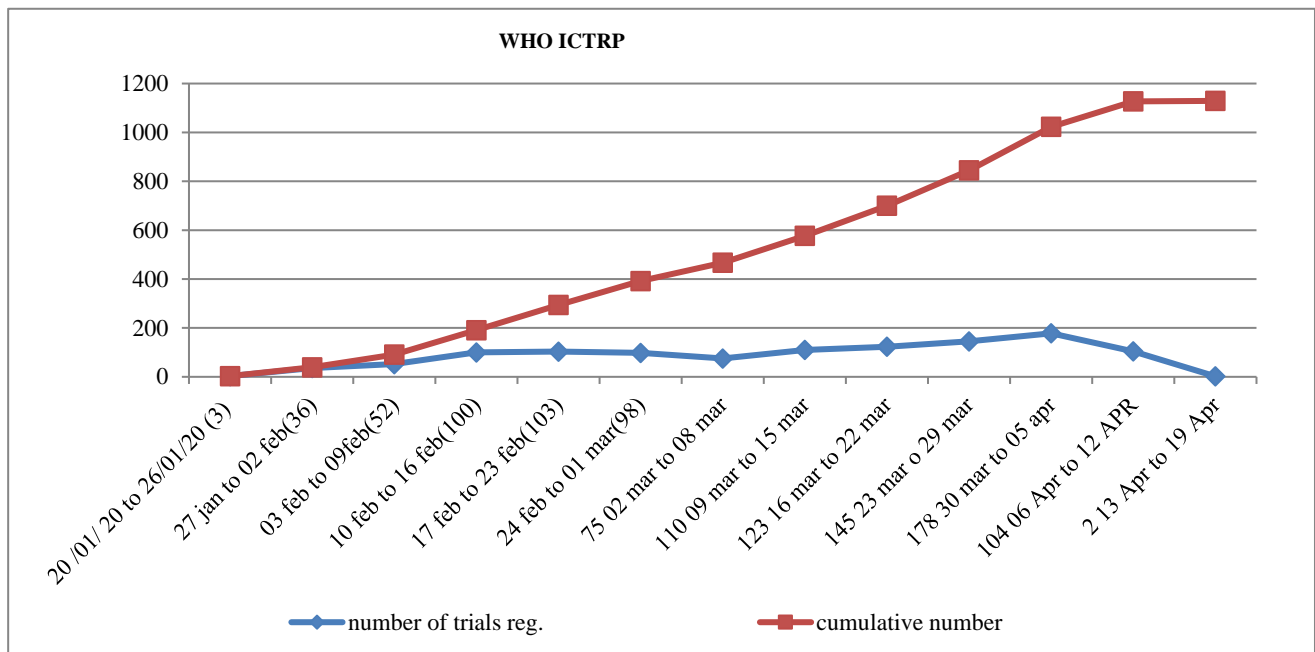


Figure 1: Trials registered in ICTRP on weekly basis (data is up to 14/04/2020).

Blue: Total no. of trials in every week. Maroon: cumulative number showing peak of trials in the week 30 march to 5th April.

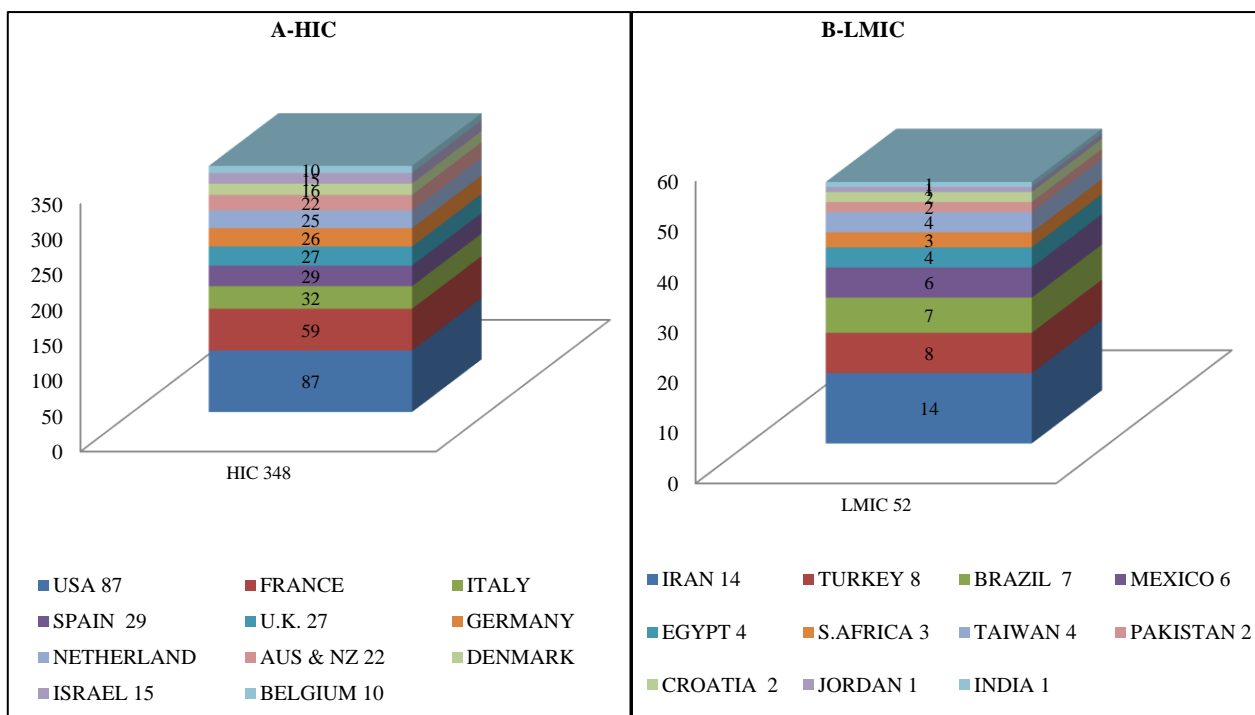


Figure 2: (A) HIC: High income country wise clinical trial distribution. (B) LMIC: low and middle income country wise clinical trial distribution, high-income countries in Europe and North America planning most of the forthcoming trials.

Interventional study type

Following data, results are derived from keyword search of public title, scientific title, intervention and primary outcome fields of the WHO-ICTRP.^{10,11}

All interventions are either medicinal AND/OR advanced therapy medicinal products.

Clinical trials are focused on chloroquine, hydroxychloroquine, and lopinavir ritonavir combination, remdesivir, favipiravir, tocilizumab and interferon.

Table 1: Ongoing clinical trials for medicinal interventions (group -wise) (n=549).

Type of medicine	No. of trials
Antiviral (nonspecific)=40	
Immunoglobulin	3
Interferon α / β / λ	29
IL-2	1
Anti IL-2	2
Novaferon	3
Emtricitabine	2
Antiviral (broad spectrum)=34	
Favipiravir	14
Triazavirin	1
Umifenovir(arbidol)	9
Oseltamivir	10
Antiviral (antiretro viral)=113	
Lopinavir + Ritonavir	49
Remdesivir	31
ASC09	4
Azvudin	3
Danoprevir (Ganovo)	3
Darunavir	2
Cobicistat	2
Danorevir	2
Tinofovir	3
Baloxivir	2
Ritonavir	7
Lopinavir	2
Ribavirin	3
Anti malarial=215	
Chloroquine	117
Hydroxychloroquine(plaquenil)	97
Mefloquine	1
Kinase inhibitors=15	
Ruxolitinib	5
Imatinib	3
Baricitinib	3
Camostat	2
Jakotinib	1
Nintednib	1
Monoclonal Antibodies=50	
Tocilizumab (Roactemra)	23
Sarilumab	7
Anakinra	5
Siltuximab	3
Camrelizumab	2
PD-1 mab	2
Pembrolizumab	1
Adalimumab	1
Eculizumab	1
Tozumab	1
Leronlimab	1
Ixkizumab	1
IFX	2

Continued.

Type of medicine	No. of trials
Immunomodulators=23	
Methyl Prednisolone	10
Dexamethasone	4
Thalidomide	2
Leflunomide	1
Fingolimod	1
Thymosin	5
Antibiotic=23	
Azithromycin	21
Nitazoxanide	2
ACE /AR modulators=14	
ACE i/ARB	10
rhACE	1
ACE 2	3
Others=26	
Vitamin C	9
Probiotic	3
Diammonium Glycyrrhizinate	3
Defibrotide	2
H2O2 gargles	2
Naproxen	2
Tanreqing	2
Polyionosinic-polycytidylic acid	1
Reduning	1
G-CSF	1

Table 2: Advanced therapy medicinal products showing convalescent plasma therapy is a promising intervention (n=91).

Advanced therapy medicinal products	No. of clinical trials
Convalescent plasma therapy	27
Human cord blood mesenchymal stem cell	13
Mesenchymal stem cell	13
Aerosol inhalation	8
Ecmo	8
Natural killer cells	7
Immunoglobulin of cured patients	3
Human umbilical cord blood mononuclear cells	3
Hyperbaric oxygen	3
Ultra short wave electrotherapy	1
Microbiota transplantation	1
Regulating intestinal flora	1
Inhaled mycobact. vaccae	1
Human menstrual blood stem cells	1
Human placenta preparation	1

Table 3: Indicating rt-pcr is a gold standard test (n=37).

Diagnostic tests	Total
rt-pcr	27
Rapid antibody test	4
Rapid antigen test	0

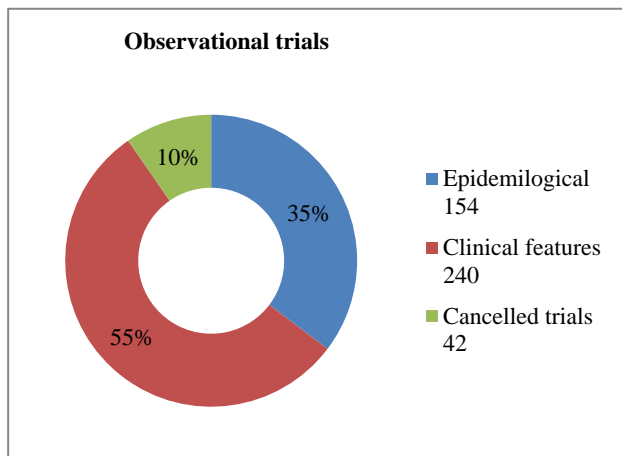


Figure 3: Observational trials study type: dominates clinical features trials.

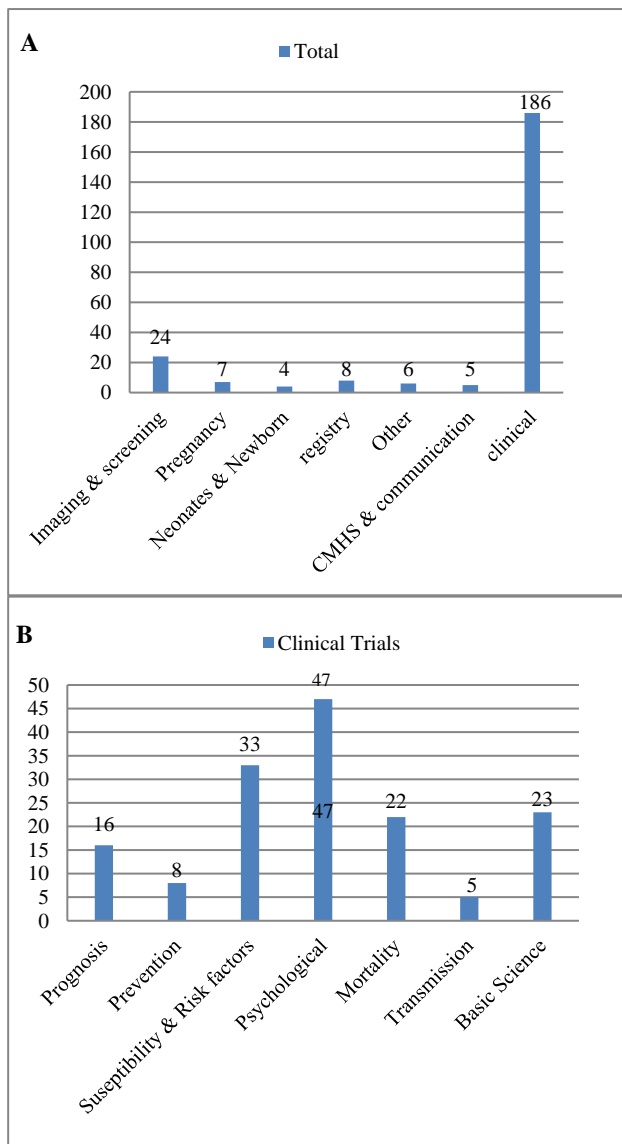


Figure 4: Clinical trials indicating (A) clinical features (B) epidemiological features showing clinical features and psychological trials are more in number.

DISCUSSION

Global response

According to Figure 1, it is seen that trials registered in WHO-ICTRP from the third week of January with a peak of trials registered in the week 30 March to 5th April with the highest number of 178 trials which is about 15.68% of the total cases.

Wuhan, China is the first epicentre of COVID-19 and outbreak originated in China. So, it is complimentary that 61% i.e. 701 including traditional Chinese medicine (TCM) of the total 1135 trials are from China.¹² The first clinical trial from China registered in ICTRP on 23rd January 2020.

Public Health Emergency of International Concern declared by WHO on 30 Jan 2020. From that moment onwards COVID-19 outbreak turned into pandemic which was declared by WHO on 11 March 2020 and the epicentre shifted to Europe and corresponding rise in clinical trials from Europe is evident from the clinical trials registered in ICTRP. The first trial from United States registered in ICTRP is on 20th February 2020.

According to Figure 2, the distribution of these clinical trials is centred in the country most affected by COVID-19 in the past 3 months, particularly China, with high-income countries in Europe and North America planning most of the forthcoming trials. Very few trials are planned in Middle East and South East Asia and South America.¹³ In this database India has only one clinical trial registered on 7th of April 2020 (as per database on 21st April 2020 with last refreshed on 14th April 2020). At the same there are 76 multi country trials.

Out of 1135 clinical trials, China has registered 701 clinical trials which comprise 61.75% of the total clinical trials. Out of remaining 434 clinical trials 80.18% trials have been registered by the high income group countries while 11.98% trials have been registered by middle and low income group countries whereas 7.83% trials are multinational.

Study type

Out of the 1135 clinical trials those were registered in ICTRP database as downloaded the database on 16th April 2020 with last refreshed on 14th April 2020, 58.32% were interventional trials, 38.42% observational trials and 3.26% were diagnostic trials.

Interventional trials (medicinal interventions)

Interventional trials are directed directly against the virus or the viral life cycle e.g. antiviral and antiparasitic; it limits the cytokine dysregulation (cytokine storm) which leads to fatal multi organ dysfunction e.g. kinase inhibitors, monoclonal antibodies with protease

inhibitors; some are immunosuppressive and immune response modulators e.g. kinase inhibitors, thalidomide and leflunomide.^{10,14}

Antiviral: There are number of antiviral molecules in intervention which are repurposed in COVID-19 trials especially those who have shown promising efficacy against SARS-CoV-1 and MERS-CoV.

Anti-parasitic: Hydroxychloroquine and chloroquine has been shown to be effective, both in vitro and clinically, against the corona virus that caused SARS in 2003-4, SARS-CoV-1.

Monoclonal antibodies and immunomodulators: There are hyper inflammatory state which causes mortality in COVID-19 patients. Above class of molecules act by reducing circulating cytokines and inflammatory modulators

Advanced therapy medicinal products

Overview: Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury.^{10,12}

ATMPs can be classified into three main types:

Gene therapy medicines: These contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;

Somatic-cell therapy medicines: These contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;

Tissue-engineered medicines: These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

Complementary and alternative medicine

There are total 98 clinical trials from complementary and alternative medicine (CAM). Of which 97 trials are from Traditional Chinese Medicine (TCM) and 1 trial is from Traditional Mongolian Medicine. Disorderly and intensive clinical trials of COVID-19 using traditional Chinese medicine and Western medicine are ongoing or will be carried out in China. However, based on the poor quality and small sample size and long completion period, we will not be able to obtain reliable, high-quality

clinical evidence about COVID-19 treatment for quite a long time in the future.^{11,15}

According to Table 1, out of 662 interventional trials maximum no. of trials about 32.33% trials are focused on the antimalarial group of medicines specifically Chloroquine and Hydroxychloroquine, 12.08% trials are focused on the antiviral group of medicines specifically Lopinavir and Ritonavir combination and Remdesivir. About 14.80% clinical trials are focused on traditional Chinese medicines (TCM). 4.38% clinical trials are focused on nonspecific antiviral group medicine Interferon. 3.47% clinical trials are focused on monoclonal antibodies group medicine tocilizumab (Roactmera) whereas 3.17% clinical trials are focused on the antibiotic group medicine Azithromycin.

According to Table 2, out of 662 interventional trials, 13.75% clinical trials are focused on the advanced therapy medicinal products of which convalescent plasma therapy clinical trials comprises of 4.07% of the total interventional trials.

Observational trials

According to Figure 3, and 4, observational trials are mainly directed to study the pattern of clinical feature, evolution of COVID-19, disease spectrum and severity of the symptoms (186). Psychological observational trials (47) access the impact of pandemic on health workers, cancer patients and COVID-19 patients and their families and especially anxiety and depression in hospital doctors and nurses.

Observational trials also studies risk factors and susceptibility (33) of COVID-19 in cancer patients, transplantation patients, myocardial infarction patients and in post surgical scenario.

The database also has clinical trials that evaluate prognosis (16) of critically ill patients (ICU) and mortality rate (22) of patients of severe pneumonia (ARDS), co-morbidities e.g. renal failure, cancer.

Imaging studies (24) are done to evaluate the efficacy of X-ray, CT scan, ultrasound and echocardiography to evaluate different aspects of disease in COVID-19 patients. There are studies on the use of telecommunication and artificial intelligence (AI) (5) for awareness, prevention, counselling and providing help to the geriatric population. Pregnant women (7), newborn and neonates (4) are also evaluated during the observational studies.

We encountered 42 cancelled studies by the investigator or cancelled due to lack of patients.

Out of 436 observational trials, 55.04% clinical trials are focused on the clinical features of COVID-19 while remaining 35.32% are epidemiological trials. Of these

154 epidemiological trials 30.51% trials are focused on the psychological aspects of the pandemic COVID-19 among health workers, patients and society and 21.42% trials are focused on risk factors and susceptibility measures. There are only 2 trials on vaccine of phase 1 study.

Diagnostic study

According to Table 3, it is observed that rt-PCR is the valid accurate, highly specific test for detection of COVID-19 antigen.¹⁶

IgM/IgG rapid antibody test although cheap and fast, it gives false positive or false negative test results and hence not considered as a gold standard diagnostic test.

Expanded access

It is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.^{17,18}

"Solidarity" clinical trial for COVID-19

"Solidarity" is an international clinical trial to help find an effective treatment for COVID-19, launched by the World Health Organization and partners. The greater the number of participating countries, the faster results will be generated.¹⁹

Clinical trials will produce potential therapies for both treatment and preventive measures of this global emergency of COVID-19 if there is high-quality specific data and vigorous statistical design.²⁰ This can be achieved through international collaboration and globalisation of clinical trials.^{13,20} The FAIR guiding principles findability, accessibility, interoperability, and reusability (FAIR) for data should be implemented, and mechanisms put in place to enable equitable use and reuse of data.²¹

CONCLUSION

COVID-19 being a new pandemic disease for which no known definitive treatment is available. This study of 1135 clinical trials reveals that these trials are for the finding the treatment of COVID-19 with very few trials on preventive aspects such as vaccine. Here we found that the clinical trials are focused on chloroquine, hydroxychloroquine, and lopinavir ritonavir combination, remdesivir, favipiravir, tocilizumab and interferon. Also, it is seen that convalescent plasma therapy is a promising intervention. Observational trials are directed mainly on the clinical features and distinguish COVID-19 from other influenza like illnesses.

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