THE TIME TO OFFER TREATMENTS FOR COVID-19

Binh T. Ngo, M.D.1,2,*
Binh.Ngo@med.usc.edu

Paul Marik, M.D., F.C.C.P., F.C.C.M.
Eastern Virginia Medical School|
Department of Internal Medicine|
Chief, Pulmonary and Critical Care Medicine|
825 Fairfax Ave, Rm 575, Norfolk, VA 23507|
marikpe@evms.edu

Pierre Kory, M.D., M.P.A
Pulmonary and Critical Care Medicine
Aurora St. Luke’s Medical Center
Milwaukee, Wisconsin .
pierrekory@icloud.com

Leland Shapiro, M.D.
Rocky Mountain Regional Veterans Affairs Medical Center in Aurora, CO and
University of Colorado Anschutz Medical Campus in Aurora, CO
Supported by The Emily Foundation in Boston, MA
lelandshapiro@cuanschutz.edu
Raphael Thomadsen, P.h.D.
Washington University in St. Louis
thomadsen@wustl.edu

Jose Iglesias, D.O., F.A.S.N.
Jersey Shore University Medical Center, Neptune NJ, Hackensack Meridian School of Medicine at Seton Hall
Jiglesias23@gmail.com

Stephen Ditmore, B.A.
Parkchester Times
stephen.ditmore@gmail.com

Marc Rendell, M.D.2,*
The Rose Salter Medical Research Foundation
Newport Coast, CA 92657
rendell@asndi.com

Joseph Varon, M.D., FACP, FCCP, FCCM, FRSM
United Memorial Medical Center
Cristina Mussini, M.D.
University of Modena and Reggio Emilia in Italy
Cristina.mussini@unimore.it

Oriol Mitja, Ph.D.
Hospital Universitari Germans Trias i Pujol
Badalona, Spain
omitja@flsida.org

Vicente Soriano, M.D. Ph.D.
UNIR Health Sciences School & Medical Center
C/ Almansa 101
Madrid 28040, Spain
Vicente.soriano@unir.net

Nicolas Peschanski, M.D., Ph.D
University Hospital of Rennes
Rennes, France
nicolas.peschanski@chu-rennes.fr

Gilles Hayem, M.D.
Hôpital Paris Saint-. Joseph, 75014
Paris, France.
ghayem@ghpsj.fr

Marco Confalonieri, M.D.
Azienda Ospedaliero-Universitaria di Trieste
Trieste, Italia
marco.confalonieri@asugi.sanita.fvg.it

Maria Carmela Piccirillo, M.D.
Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale
Napoli, Italia
m.piccirillo@istitutotumori.na.it

Antonio Lobo-Ferreira, M.D., Ph.D.
Unidade de Investigação Cardiovascular (UniC), Faculdade de Medicina
da Universidade do Porto, Centro Hospitalar Universitário de São João,
Porto, and Hospital Rainha Santa Isabel, Marco de Canaveses, Portugal
Aloboferreira@gmail.com

Iraldo Bello Rivero M.Sc., Ph.D.
Department of Clinical Investigations
Center for Genetic Engineering and Biotechnology,
Ave 31 e/ 158 and 190. Cubanacan, Playa, 10600
Havana, Cuba.
iraldo.bello@cigb.edu.cu

Eivind H. Vinjevoll, M.D.
Volda Hospital HMR, Norway.
Eivind.vinjevoll@gmail.com

Daniel Griffin, M.D., Ph.D.*,3
ProHEALTH, an OPTUM Company
  Columbia University
College of Physicians and Surgeons
Email: danielgriffinmd@gmail.com

Ivan FN Hung, MBChB, M.D., MRCP, FRCP.*,3
Li Ka Shing Faculty of Medicine
University of Hong Kong
Ivanhung@hku.hk

1 From the Keck Medical School of USC
2 From the Rose Salter Medical Research Foundation
3 CoSenior author
* Corresponding author
BACKGROUND  As of January 1, 2021, there have been 81,947,503 confirmed cases of COVID-19, resulting in 1,808,041 deaths worldwide. Several vaccines are now available for emergency use, but it will take many months to immunize the world’s population. There is a pressing need for outpatient treatment now. We reviewed the possible options.

METHODS We reviewed up-to-date information from several sources to identify potential treatments to be utilized now for COVID-19. We searched for all ongoing, completed and published trial results with subject numbers of 100 or more, and used a targeted search to find announcements of unpublished trial results.

RESULTS

As of December 27, 2020, we identified 750 trials currently in recruitment phase. Of these, 122 were directed at prevention in healthy individuals, 100 were classified as treatment of outpatients with documented infection, and 390 were for treatment of hospitalized inpatients. There were 9 trials focusing on the post discharge Tail phase. Among the trials, there were 60 vaccine trials, 120 trials of hydroxychloroquine, 33 trials of alternative therapy, 12 trials of colchicine, 38 trials of anticoagulants, 22 trials of the RNA polymerase inhibitor favipiravir (FVP), 19 trials of interferons, 18 trials of glucocorticoid, and 58 trials of plasma based products. Closure of enrollment was projected by the end of the year for 153 trials. We found 83 publications reporting findings in human studies on 14 classes of agents, and on 7 vaccines. There were 45 randomized or active controlled studies, the rest retrospective observational analyses. Most publications dealt with hospitalized patients, only 18 publications in outpatients. Remdesivir, convalescent plasma, and synthetic anti-spike protein antibodies have been granted emergency use authorization in the United States. There is also support for glucocorticoid treatment of the COVID-19 respiratory distress
syndrome. There is data supporting the use of several antiviral medications, some of which are in use in other countries.

CONCLUSION. Vaccines and antibodies are highly antigen specific. There is a need for antiviral agents in addition to mass immunization. It will be necessary for public health authorities to make hard decisions, with limited data, to prevent the continued spread of the disease and deaths.
1. INTRODUCTION

SARS-CoV-2 spread with extraordinary speed from its origin in December 2019 in Wuhan, China. As of January 1, 2021, there have been 81,947,503 confirmed cases of COVID-19, resulting in 1,808,041 deaths worldwide affecting 220 countries and territories (1). Symptomatic COVID-19 exhibits a characteristic sequence of phases related to the primary viral attack, manifesting as an influenza-like illness, affecting 80% of infected individuals. Then, in patients destined for severe disease, within seven to 10 days of onset of symptoms, an organizing pneumonia develops which requires assisted mechanical ventilation in up to 5% of patients (See Figure 1) (2,3). Elevated cytokines and a coagulopathy at this pulmonary stage suggests an immune reaction as probable cause (4,5).

In mainland China, vigorous efforts to contain the spread of COVID-19 by home isolation, closure of business activity, travel bans, and tracking and control of contacts succeeded. As of December 10, China has had 96,762 confirmed cases and 4,789 deaths, but the number of new cases has been low since April (1). Similar measures contained the epidemic in Taiwan and in New Zealand (1). However, the disease has not been controlled in the rest of the World, particularly Europe where there have been 26,490,355 cases with 582,016 deaths and the United States (USA) where, despite only a fifth of the population of China, there have been 19,746,390 confirmed cases of COVID-19 and 335,789 deaths. (1). In the Western World, as in China, the response to the pandemic was through reduction of person-to-person contact. Beginning in early March, social gatherings and meetings ended; schools and businesses were closed along with recreation areas, parks, and beaches. These social distancing efforts blunted the spread of the
disease, but not with the results achieved in China. Due to economic pressures, epidemiologic containment was relaxed resulting in a significant ongoing surge well surpassing the original April peak.

The major industrialized countries have made an unprecedented effort to rapidly develop vaccines for COVID-19. Two mRNA vaccines have demonstrated 90% effectiveness at two months post immunization, and mass vaccination has begun. However, in view of the continuing daily increase in new cases and deaths, we believe that it is unwise to place sole reliance on immunization alone. Our goal was to assess the options at the present time for release of pharmacologic agents to treat and to prevent COVID-19 while pursuing widespread vaccination in 2021.

2. METHODS

2.1 CLINICAL TRIALS: We reviewed up-to-date information from multiple sources to identify potential treatments for COVID-19: The Reagan-Udall Expanded Access Navigator COVID-19 Treatment Hub was used to track the efforts of companies to develop therapeutic interventions. We searched for investigational trials in active recruitment and those that have completed enrollment. We used (A) covid-trials.org, a registry to collate all trials in real time with data pulled from the International Clinical Trials Registry Platform and all major national registries (6). We cross validated information on (B) clinicaltrials.gov, the registry of clinical trials information maintained by the United States National Library of Medicine. We further cross referenced the trials on (C) the World Health Organization’s International Clinical Trials Registry Platform (WHO ICTRP), and (D) (Cochrane COVID-19 Study Register. We excluded studies which were clearly observational with multiple different treatments, with no means of
comparison. We further set a cutoff of 100 for numbers of subjects since smaller trial size typically lacks statistical power to enable regulatory approval. For each trial selected, we documented the setting of patient contact, either hospital or outpatient, the type of control procedure, the date the trial was initially registered, and the proposed date of completion of enrollment.

2.2 PUBLISHED TRIAL RESULTS: Our search was carried on the week of December 27, 2020. We identified all publications on pubmed.gov to find peer reviewed articles, on medRxiv to find preprint reports and the WHO Global Literature on Coronavirus Disease. We further carried out daily Google™ searches on each potential treatment to find preliminary reports, typically presented as press releases, reviewed by a journalist. We included all publications in our results as well as trial results posted as complete on Clinicaltrials.gov. We did not exclude trials with less than 100 subjects, since many reports were interim, with trials ongoing.

2.3 VIRTUAL DISCUSSIONS AMONG CO-AUTHORS: We used the preprint server medRxiv to post a systematic analysis of the development of therapeutic interventions for COVID-19 in order to stimulate diffusion of the manuscript and allow widespread “open source” input from co-authors (7). Successive versions of the preprint article have been posted periodically as a chronicle beginning in late May, 2020 and continuing to date (8). This process led to the present multinational consensus process involving 36 co-authors.

3. RESULTS
3.1 REVIEW OF CURRENT TRIALS: As of December 27, 2020, we identified 750 trials currently in recruitment phase with subject size of 100 or more (Supplementary Table 1). Of these, 122 were directed at prevention in healthy individuals, 100 were classified as treatment of outpatients with documented infection, and 390 were for treatment of hospitalized inpatients. There were 9 trials focusing on the post discharge Tail phase. The remaining trials were unclear as to intended subjects. Among the trials, there were 60 vaccine trials, 120 trials of hydroxychloroquine (HCQ), 33 trials of alternative therapy, 12 trials of colchicine, 38 trials of anticoagulants, 22 trials of the RNA polymerase inhibitor favipiravir (FVP), 19 trials of interferons, 18 trials of glucocorticoid, and 58 trials of plasma based products. Closure of enrollment was projected by the end of the year for 153 trials.

3.2 COMPLETED TRIALS: As of December 27, 2020, there were 97 trials reporting completion with 100 or more subjects (Supplementary Table 2). There were 52 trials in hospitalized patients, 9 directed at outpatients, and 12 prevention studies, the rest mixed.

3.3 PUBLISHED RESULTS ON COVID-19 TRIALS: As of December 27, 2020 we found 83 publications reporting findings in human studies on 14 classes of agents, and on 7 vaccines (See TABLE 1). There were 45 randomized or active controlled studies. The rest were retrospective observational analyses. Only 15 publications dealt with outpatient care, including 7 vaccine reports; the rest were all in hospitalized patients.

3.3.1 In the group of antiviral agents, the largest published randomized, controlled trials were with the intravenously administered RNA polymerase inhibitor remdesivir (9-13). A double blind, randomized placebo controlled trial of remdesivir, in 1062 moderate to severely ill patients was carried out by the National Institute of Allergy and Infectious Disease (NIAID) (10). The patients who received remdesivir had a median recovery time of 10
days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001). The Kaplan-Meier estimates of mortality by 29 days after randomization were 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). On the basis of this trial, the Food and Drug Administration (FDA) approved the use of remdesivir for COVID-19 hospitalized patients. A different study of remdesivir in hospitalized patients with moderate COVID-19 clinical status showed improved clinical status by day 11 compared to standard of care for a 5 day course of remdesivir, but not for a 10 day course (12). There has been no data provided on viral clearance for the U.S. remdesivir studies. In early April, the WHO organized a megatrial, appropriately named Solidarity, to assess four separate treatment options only in hospitalized patients: (a) Remdesivir, an intravenously administered inhibitor of RNA polymerase; (b) The HIV agent lopanovir/ritanovir (LPV/R); (c) LPV/R plus Interferon β-1a; and (d) the antimalarials hydroxychloroquine (HCQ) and chloroquine (13). Results of the Solidarity Trial were reported by the World Health Organization on October 15, 2020. They found no effect of remdesivir on 28 day mortality, need for mechanical ventilation nor duration of hospitalization in a study including 5451 hospitalized patients (13).

3.3.2 There were two positive randomized, active control clinical trials in China of the orally administered RNA polymerase inhibitor favipiravir (FVP) (14,15). In a trial comparing 116 patients on FVP to 120 on umifenovir, the 7 day clinical recovery rate was 55.9% for the umifenovir group and 71% in the FVP group (15). In Russia, a preliminary study of FVP showed reduced duration of viral shedding, and the drug was approved for clinical treatment beginning in multiple hospitals on June 12, 2020 (17). In a follow-up phase 3 study, they reported 27% clinical improvement at day 10 compared to 15% for standard care with 98% clearance of SARS-COV-2 compared to 79% (18). In India, a study of 150 mild to moderate COVID-19 patients showed median time to clinical cure of 3 days (95% CI: 3 days, 4 days) for FVP versus 5 days (95% CI: 4 days, 6 days).
for control, $P=0.030$, and FVP was approved to treat COVID-19 in July (19). In late September, a report, still unpublished, of a randomized controlled study in Japan announced more rapid viral clearance in FVP treated patients.

3.3.3 There have been many studies of HCQ (20-47). A group in Marseille reported their experience with 3737 patients screened positive for SARS-CoV-2 and immediately treated with HCQ and azithromycin (AZM), after excluding patients at risk of QT prolongation (20). They showed clearance of viral shedding in 89.4% of the patients by ten days. The overall mortality in their population was 0.9%, none in patients under 60 years old, and no sudden cardiac deaths. They had no randomized control population, but their study prompted immediate widespread use of HCQ throughout the world for treatment of COVID-19 patients.

Subsequent randomized controlled studies in hospitalized patients have shown no clinical nor mortality benefit of HCQ. In the randomized RECOVERY trial in 1542 hospitalized patients in the United Kingdom, there was no significant difference in the primary endpoint of 28-day mortality (26.8% HCQ vs. 25% usual care; hazard ratio 1.09 [95% confidence interval 0.96-1.23]; $P=0.18$) (34). In the Solidarity Trial, there was no benefit of HCQ on mortality (HCQ RR=1.19 [0.89-1.59, $P=0.23$; 104/947 vs 84/906), need for mechanical ventilation, nor duration of hospitalization (13). However, in a retrospective comparison study at NYU Langone Health for all patients admitted between March 2 and April 5, 2020, there was a move to add zinc 100 mg daily to their standard HCQ plus AZM regimen (35). There was a significantly lower mortality (13.1%) among the zinc treated patients compared to those who did not receive zinc (22.8%).
There has been limited study of HCQ in outpatients. In one internet-based prevention study, with HCQ given for 5 days to healthy individuals with a significant exposure to SARS-Cov-2, the incidence of new illness compatible with COVID-19 did not differ significantly between participants receiving HCQ (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); absolute difference −2.4 percentage points (95% confidence interval, −7.0 to 2.2; \( p = 0.35 \)) (36). The same group also treated 423 patients with mild symptoms imputed to COVID-19 (37). At 14 days, 24% (49 of 201) of participants receiving HCQ had ongoing symptoms compared with 30% (59 of 194) receiving placebo (\( p = 0.21 \)).

A study in Spain of 293 patients with PCR-confirmed mild COVID-19, found no difference in viral load nor risk of hospitalization following 6 days of HCQ treatment compared to untreated patients (38). The same group treated 1,116 healthy contacts of 672 Covid-19 index cases with HCQ while 1,198 were randomly allocated to usual care (39). There was no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54-1.46]), nor evidence of prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ).

A large population study in Portugal surveyed all patients on chronic HCQ treatment and cross-verified against a mandatory database of patients registered with COVID-19 (40). The incidence of a positive PCR test for SARS-CoV-2 infection in patients receiving HCQ was 5.96%, compared to 7.45% in those not so treated, adjusted odds ratio 0.51 (0.37-0.70). However, two separate randomized controlled studies found no evidence of benefit of two months prophylactic treatment of hospital workers with HCQ (41,42).

**3.3.4**. Published results with Lopanovir/ritonavir (LPV/r) have been disappointing (13, 43-45). In a randomized trial with 99 patients on LPV/r and 100 receiving standard care, there was no difference in time to clinical improvement, mortality nor viral clearance (44). In the RECOVERY trial in
1,596 hospitalized patients there was no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; \( p=0.58 \) (45). In the Solidarity Study, there was no effect of LPV/r on 28 day mortality LPV/r RR=1.00 (0.79-1.25, \( p=0.97 \); 148/1399 vs 146/1372), need for mechanical ventilation nor duration of hospitalization (13).

A possibly more favorable result was obtained in Hong Kong in a study of 86 patients assigned to triple combination therapy with LPV/r plus ribavirin plus interferon-\( \beta \)-1 (46). Compared to a control group of 41 patients receiving LPV/r alone, the combination group had a significantly shorter median time from start of study treatment to negative SARS-Cov-2 nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], \( p=0.0010 \). The time to complete alleviation of symptoms was 4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3.92 [95% CI 1.66–9.23. This study was interpreted not as supporting LPV/r therapy, but rather focusing on interferon-\( \beta \)-1 as the primary treatment modality.

### 3.3.5 Interferon studies have been encouraging.

In Cuba, a combination of interferon-\( \alpha \)-2b and interferon \( \gamma \) on background therapy of LPV/r and chloroquine was successful in achieving viral clearance in 4 days in 78.6% of the patients compared to 40.6% of those receiving interferon-\( \alpha \)-2b alone (49). In the Solidarity Study in hospitalized patients, there was no effect of injected interferon on 28 day mortality (IFN RR=1.16 (0.96-1.39, \( p=0.11 \); 243/2050 vs 216/2050), need for mechanical ventilation nor duration of hospitalization (13). However, a separate trial of nebulized interferon \( \beta \)-1 reported positive improvement in clinical status (52).
3.3.6 There have been many observational studies of immunomodulatory therapy with the IL-6 inhibitor tocilizumab and the IL-1 inhibitor anakinra to mitigate the pulmonary phase of COVID-19 suggesting reduction of mortality and need for intubation in hospitalized severe and critically ill patients (28, 53-66). However, in several randomized control studies, there has been no benefit with tocilizumab (67-69). In the COVACTA trial, there was no benefit of tocilizumab in clinical status, mortality (19.7% tocilizumab vs placebo = 19.4%), nor in ventilator free days (68), and in the Cor-Immuno-Toci trial, no decrease in mortality at day 28 (69). The tocilizumab results in these randomized controlled trials were affected by a higher frequency of glucocorticoid use in the control groups.

3.3.7 Pre-COVID-19, glucocorticoid treatment had been a recognized treatment with mortality benefit for patients in severe respiratory distress (70). Dexamethasone has now demonstrated benefit in several COVID-19 hospital trials (71-72). In the RECOVERY trial, 2104 patients were randomly allocated to receive dexamethasone for ten days compared to 4321 patients concurrently allocated to usual care (72). Overall, 454 (21.6%) patients randomized to dexamethasone and 1065 (24.6%) patients receiving usual care died within 28 days (age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; \( p < 0.001 \)). Dexamethasone reduced deaths by one-third in the subgroup of patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; \( p < 0.001 \)) and by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; \( p = 0.002 \)), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; \( p = 0.14 \)). Most trials of other glucocorticoids have shown similar benefits in COVID-19 patients with acute respiratory failure (73-80).
3.3.8 There is promising data on convalescent plasma (81-86). A meta-analysis including 4173 patient outcomes across a multinational series of studies concluded that convalescent plasma treatment yielded a 57% reduction in mortality (85). The reduction was greatest in patients treated within 3 days of diagnosis with high titer antibody plasma. Based on evidence of safety in over 20,000 patients in an expanded access program coordinated by the Mayo Clinic, the U.S. FDA recently issued an emergency authorization for use of convalescent plasma (86). Monoclonal antibodies to the SARS-COV-2 spike protein have been synthesized. Treatment of ambulatory patients with the LY-CoV555 neutralizing antibody and the Regeneron combination of two antibodies early in the course of infection has shown success in reducing the frequency of hospitalization, and the FDA issued an emergency authorization for use in outpatients (88).

3.3.9 There have been a number of reports on agents not ordinarily considered as antivirals. These include famotidine, nitazoxanide, fluvoxamine, colchicine, and ivermectin (89-96). Colchicine, an anti-inflammatory agent, suggested benefit in the GRECCO, placebo-controlled, randomized clinical trial of 105 patients (90). The primary clinical end point of deterioration to mechanical ventilation or death was 14% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01-0.96; p = 0.02). There have now been a number of trials including several randomized controlled studies suggesting benefit with ivermectin both in prevention and in treatment of COVID-19 (TABLE 1).

3.3.10 A number of vaccines have reported successful induction of neutralizing antibody and cellular immune responses in early phase trials (98-104). The Moderna and Pfizer Biontech mRNA spike protein vaccines released data showing over 90% effectiveness at preventing symptomatic infection in a 2 month post immunization observation period, and emergency authorization for immunization has been given. Massive vaccinations have begun in many countries.
4. CONCLUSION

SARS-Cov-2 fueled by modern day jet travel overwhelmed medical preparedness for the pandemic. Current projections are for a continuation of new cases and deaths continuing in 2021 (105,106). On December 31, 2020, 470,046 new cases were reported worldwide (1). Of these 174,814 cases occurred in the United States. Clinical trials to date have focused primarily on hospitalized patients to try to prevent death. It is hoped that the use of remdesivir, convalescent plasma, glucocorticoids, anticoagulation and improved management of COVID-19 respiratory failure will lower the present rate of in hospital mortality which in some series has been as low as 6% but in most hospitals still approaches 20% (77). However, it is essential to change the present dynamic of attempted therapeutic responses to recognize specific phases of the disease (107). In particular, efforts must now focus on prevention and treatment of the initial viral infection so that hospitalization can be avoided. We face a dilemma with inadequate current prevention and treatment for outpatients with mild to moderate disease, constituting 80% of the infected population and the primary mode of spread of SARS-Cov-2. The lessons learned in very sick hospitalized patients do not necessarily apply to the earlier viremic phase. Antiviral agents, such as remdesivir and favipiravir, interferon, convalescent plasma, and monoclonal antibodies are likely to be most effective during the early stage of viremia, which is prior to the pulmonary phase requiring hospitalization.

Vaccines have been the solitary hope held out by public health authorities to arrest SARS-Cov-2. Progress on vaccine development has been rapid, but the speed of development does not reduce the challenges of developing vaccines to be administered to the population of the entire World. Although neutralizing antibodies and memory T cells can be produced by the vaccine candidate, the demonstration of true protection requires long-term
follow-up of an exposed vaccinated population. The current vaccines will be released for emergency use after only a short two month period of observation. No matter how rapidly a vaccine advances to Phase III testing, the duration of follow-up cannot be shortened, and for SARS-Cov-2 possibly prolonged due to several factors. First, there is a risk of immune enhancement of infection which occurs when induced antibodies increase entry and internalization of virus into myeloid cells (108). This major complication struck the newly developed dengue vaccine in 2017 (109). Second, the sinister autoimmune pathogenicity of SARS-Cov-2 raises the risk of delayed long-term harm if the virus is not fully and immediately eradicated by the initial immune response to the vaccine. Furthermore, studies of recurrent coronavirus infections suggest that infection may confer immunity for less than a year (110). After implementation of a new vaccine, efforts to find volunteers for trials of new, more effective vaccines will be hampered if there is no treatment available for placebo treated patients who become infected. Vaccines are specific to the intended pathogen. There is the risk that the virus will mutate to a form for which the new vaccine may not be fully protective. Already two variants have emerged and caused major outbreaks. The level of protection offered by the current vaccines is currently under study. Finally, the degree of acceptance of the COVID-19 vaccines by the general population is questionable. Seasonal influenza vaccination coverage was only 48% in 2019 (111). Children typically have limited COVID-19 symptoms. However, they may serve as a reservoir of ongoing infectivity (112). Currently there have been no clinical trial results of vaccine in children.

It also follows that totally new viruses may emerge just as did SARS-Cov-2. COVID-19 is now the sixth severe viral epidemic to hit mankind in the past 20 years; certainly it has been more widespread than SARS-Cov-1, H1N1 influenza, MERS, Zika, and Ebola, but that does not diminish the gravity of these repeated viral threats. Development of antigen specific vaccines takes a long time during which disease takes a large toll as has been the case for SARS-Cov-2. The succession of viral afflictions points to the need to implement widespread use of antiviral agents. The current recom-
mendation for COVID-19 is home quarantine with no specific treatment for patients with suspicious symptoms. What is needed is therapeutic inter-
vention which can be used to treat all outpatients with positive COVID-19 tests at the time of initial symptoms, not waiting for deterioration requiring
hospital care. Hydroxychloroquine has not succeeded. Remdesivir administered intravenously for five days is not a practical daily outpatient treat-
ment; Gilead© is attempting to develop an inhaled remdesivir formulation, but those efforts are only now beginning. Favipiravir, a tablet, could be
used in early stages of infection and has now been released in Russia, Hungary, and in India, but not in the United States and the European Union. It
has known embryogenic risks, so its use requires restrictions on women of childbearing potential, as is the case with tretinoin for acne and thalido-
mide for multiple myeloma. Trials with camostat, the serine protease inhibitor, capable of blocking cell entry of SARS-Cov-2, are not due to end till
the fourth quarter of the year. Similarly, a prevention trial with colchicine is not scheduled to end until the fourth quarter of 2020. Convalescent
plasma is used primarily in hospital patients. Monoclonal antiviral neutralizing antibodies based on the same principle have finally received emer-
gency use authorization for ambulatory patients. However, the scale of production of these monoclonal antibodies is far too limited to offer to all
outpatients who should be treated. Interferon formulations have shown promise in several studies. There have been several randomized controlled
studies suggesting benefit with ivermectin both for prophylaxis and treatment.

Yet, at this time, no outpatient therapy has been proven safe and effective in large scale phase III randomized, placebo-controlled studies. There are
strong arguments to avoid emergency use of agents until trials are completed and analyzed, but the agents suggested are not new. Most are drugs like
ivermectin, colchicine, and the interferons, marketed and available for other conditions and with well-known safety profiles. There is a clear need to
offer outpatient therapeutic intervention now to the World’s population.
There is a precedent to resolve the conflict between immediate clinical need and the requirements for rigorous controlled trials to prove efficacy. We should remember that the greatest success in fighting a pandemic occurred over the past two decades in the battle against the HIV virus which causes AIDS. AIDS was first recognized in 1981 in the MSM (men who have sex with men) community. The disease was considered a death sentence. There was widespread fear because there was no treatment, and projections of infection escalated into the millions. The first AIDS remedy was azidothymidine (AZT), synthesized in 1964 in the hope that it would combat cancer. Twenty years later Dr. Samuel Broder, head of the National Cancer Institute, showed that the drug had activity against the HIV virus in vitro (113). Burroughs Wellcome launched a rapidly conceived trial with just 300 patients. They stopped the trial in 16 weeks claiming that more patients survived on AZT. The FDA came under enormous pressure from AIDS activists to make the drug available, and it was approved on March 19, 1987, with only that one trial. It had taken 20 months for the FDA to give approval to release the drug. To this day, the design and results of the trial remain controversial.

The LGBT community continued to battle for early release of other medications to combat the AIDS pandemic. On October 11, 1988, a massive protest occurred at the FDA. It was back then Dr. Anthony Fauci who publicly advanced the idea of a parallel track to make drugs widely available even while studies are progressing: “Clearly, the standard approach to the design of clinical trials—that is, rigid eligibility criteria as well as the strict regulatory aspects that attend clinical trial investigations and drug approval—was not well-suited to a novel, largely fatal disease such as this with no effective treatments, and we had many intense discussions about how to make that approach more flexible and ethically sound. One example, which I and others worked closely with the AIDS activists to develop, was called a parallel track for clinical trials. The parallel track concept, which the United States Food and Drug Administration ultimately came to support, meant that there would be the standard type of highly controlled admission criteria and data collection for the clinical trial of a particular drug. In parallel, however, the drug also could be made available to those who
did not meet the trial’s strict admission criteria but were still in dire need of any potentially effective intervention, however unproven, for this deadly disease” (114).

The parallel track advocated by Dr. Fauci was adopted. Today, there are 41 drugs or combinations approved by the FDA to treat and to prevent HIV infection. There is still no vaccine. There are now an estimated 1.1 million patients with HIV in the United States, most enjoying near normal life expectancy thanks to the antiviral agents. The CDC has contributed greatly to limit the spread of HIV by advocating safe sex practices, but social distancing is not the norm for HIV. Rather “treatment as prevention” for people with HIV using highly active antiretroviral regimens to prevent transmission as well as pre-exposure prophylaxis with a daily antiviral combination pill are currently endorsed by the CDC and adopted in wide segments of the at risk population (115).

In this pandemic crisis, we appeal to public health authorities to change the dynamic of current studies to outpatient care and to cross institutional, commercial and international boundaries to collate and combine all randomized controlled data submitted for all agents in Europe, China, Russia, Japan, India and other countries, and by competing companies, whether officially published, posted on line, or unpublished to finalize confirmatory results. The Solidarity Trial is a model of what could and should be done to unify a worldwide effort to pursue randomized controlled studies in outpatients. At the same time, agents with favorable preliminary results and no safety issues should be made available through a parallel track. In Russia and India, the parallel track has been fully implemented, with FVP now offered as treatment throughout both countries, even as further confirmatory controlled trials proceed. Interferon formulations are now approved treatments in China and Cuba. It is reasonable to authorize vaccination in very large parallel track studies in at risk populations, such as healthcare workers and the elderly. At this time, with no other option available, vaccination will have to be universal, despite the need to perform controlled studies to develop improved vaccines. However, it is unwise to rely
solely on the hope for eventual mass vaccination to stop SARS-Cov2. Antiviral medication has succeeded in limiting HIV and hepatitis, and antivirals are just as important as annual vaccination for control of influenza. It is necessary for public health authorities to make hard decisions now despite limited current data and offer outpatient treatments on a broad front with no further delay.

REFERENCES

1) WHO Coronavirus Disease (COVID-19) Dashboard
Data last updated: 2021 January 1 11 am.

2) Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-1242

3) Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.

4) Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19.
5) Ricardo J, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation storm: Lancet Respir Med 2020; 8(6): e46-e47

6) Thorlund KT, Dron L, Park J et al. A real-time dashboard of clinical trials for COVID-19. Lancet Digital Health 2020; 2: e86-e87 published on line 24 Apr 20 https://doi.org/10.1016/S2589-7500(20)30086-8

7) Ngo BT, Rendell M. A systematic analysis of the time course to develop treatments for COVID-19 medRxiv 2020.05.27.20115238; doi: https://doi.org/10.1101/2020.05.27.20115238

8) Ngo BT, Marik P, Kory P, et al. The time to offer treatments for COVID-19. medRxiv, 16 Dec20 doi: https://doi.org/10.1101/2020.05.27.20115238

9) Wang Y, Zhang D, Guanhua Du G, et al. Remdesivir in adults with severe COVID-19: a randomised,double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395 (10236): 1569-1578
10) Beigel JH, Tomashek KM, Dodd LE et al. Remdesivir for the Treatment of Covid-19 — final Report. October 8, 2020 DOI: 10.1056/NEJMo2007764

11) Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. New Engl J Med May 27, 2020 DOI: 10.1056/NEJMo2015301

12) Spinner CD, Gottlieb RL, Criner GJ et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19. A randomized clinical trial. JAMA. Published online August 21, 2020. doi:10.1001/jama.2020.16349

13) WHO Solidarity trial consortium. Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results. medRxiv 2020. https://doi.org/10.1101/2020.10.15.20209817 posted Oct 15, 2020

14) Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: An open-label control study. Engineering (Beijing). 2020;10.1016/j.eng.2020.03.007. doi:10.1016/j.eng.2020.03.007

15) Chen C, Huang J, Zhenshun Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. medRxiv preprint doi: https://doi.org/10.1101/2020.03.17.20037432. this version posted March 20, 2020.
16) Preliminary Report of the Favipiravir Observational Study in Japan Favipiravir Observational Study Group.

http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf Accessed 19 June 2020

17) Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for treatment of patients with moderate COVID-19: Interim results of a Phase II/III multicenter randomized clinical trial. Clinical Infectious Diseases, ciaa1176, https://doi.org/10.1093/cid/ciaa1176

18) https://clinicaltrials.gov/ct2/show/NCT04542694: Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19. Results posted 9 Nov 2020

19) Udwadia ZF, Singh P, Barkate H, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infec Disease (In Press)

20) Lagier JC, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis. 2020 July-August; 36: 101791. Available on line 25 June 2020

21) Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv preprint doi: https://doi.org/10.1101/2020.03.22.20040758. this version posted March 30, 2020.

22) Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19) J Zhejiang Univ (Med Sci) 2020, Vol. 49 Issue (1): 0-0 DOI: 10.3785/j.issn.1008-9292.2020.03.03
23) Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. BMJ 2020;369:m1849

24) Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. Med (2020), https://doi.org/10.1016/j.medj.2020.06.001

25) Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. New Engl J Med 2020;382(25):2411-2418

26) Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323(24): 2493-2502.

27) Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020;369:m1844

28) Ip A, Berry DA, Hansen E, et al, Hydroxychloroquine and tocilizumab therapy in COVID-19 patients - An observational study. PLoS ONE 15(8): e0237693.
29) Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Inf Dis. 2020; 97: 396–403

30) Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. New Eng J Med published on line July 23, 2020 DOI: 10.1056/NEJMo2019014

31) Furtado RHM, Berwanger O*, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 2020; 396: 959–67

32) 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 Apr 24;3(4):e208857. doi: 10.1001/jamanetworkopen.2020.8857.

33) Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19 A randomized clinical trial. JAMA. Published online November 9, 2020. doi:10.1001/jama.2020.22240

34) RECOVERY Collaborative Group. Effect of Hydroxychloroquine in hospitalized patients with COVID-19. New Engl J Med October 8, 2020 DOI: 10.1056/NEJMo2022926
35) Carlucci P, Tania Ahuja T, Petrilli CM, et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients medRxiv doi: https://doi.org/10.1101/2020.05.02.20080036

36) Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med J 2020; 383:517-525

37) Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. A randomized trial. Ann Int Med 2020 Jul 16 : M20-4207

38) Mitjà O, Corbacho-Monné M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clinical Infectious Diseases, ciaa1009, https://doi.org/10.1093/cid/ciaa1009 Published: 16 July 2020

39) Mitjà O, Ubals M, Corbacho-Monné M, et al. A cluster-randomized trial of hydroxychloroquine as prevention of Covid-19 transmission and disease. medRxiv 2020.07.20.20157651; doi: https://doi.org/10.1101/2020.07.20.20157651

40) Ferreira A, Oliveira-e-Silva A, Bettencourt P. Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection. J Med Virol 2020;1-5J Med Virol. 2020;1–5 DOI: 10.1002/jmv.26286
41) Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers. A randomized clinical trial
JAMAInternMed.doi:10.1001/jamainternmed.2020.6319 PublishedonlineSeptember30,2020.

42) Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a ran-domized trial. Preprint. medRxiv. 2020;2020.09.18.20197327. Published 2020 Sep 18. doi:10.1101/2020.09.18.20197327

43) Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI.Med (N Y). 2020 May 19 doi: 10.1016/j.medj.2020.04.001

44) 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):1787-1799.

45) RECOVERY Collaborative Group. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Published Online October 5. 2020 https://doi.org/10.1016/S0140-6736(20)32013-4.
46) Hung IFN , Lung KC, Tso EYK et al Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial Lancet,2020 May 30;395(10238):1695-1704.

47) Estebanez M, Ramirez-Olivencia G, Mata T, et al. Clinical evaluation of IFN beta-1-b in COVID-19 pneumonia: a retrospective study. MedRxiv doi: https://doi.org/10.1101/2020.05.15.20084293

48) Pereda R, González D, Rivero HB, et al. Therapeutic effectiveness of interferon-alpha 2b against COVID-19: the Cuban experience. medRxiv preprint doi: https://doi.org/10.1101/2020.05.29.20109199.

49) PE Idelsis, Perez-Escribano J, Duncan-Robert Y, et al Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA medRxiv https://doi.org/10.1101/2020.07.29.20164251

50) Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. Int Immunopharmacol. 2020 Nov; 88: 106903. Published online 2020 Aug 24. doi: 10.1016/j.intimp.2020.106903

51) Meng Z, Wang T, Chen L, et al. An experimental trial of recombinant human interferon alpha nasal drops to prevent COVID-19 in medical staff in an epidemic area. medRxiv .https://doi.org/10.1101/2020.04.11.20061473
52) Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med 2020 Published Online November 12, 2020
https://doi.org/10.1016/S2213-2600(20)30511-7

53) Xua X, Hanb M, Lia T, et al. Effective treatment of severe COVID-19 patients with tocilizumab 10970–10975 | Proc Natl Acad Sci | May 19, 2020 | vol. 117 | no. 20 www.pnas.org/cgi/doi/10.1073/pnas.2005615117

54) Somers EC, Eschenauer GA, Troost JP. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. MedRxiv doi: https://doi.org/10.1101/2020.05.29.20117358

55) Rossi B, Nguyen LS, Zimmermann, et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study medRxiv doi: https://doi.org/ 10.1101/2020.06.06.20122341

56) Martinez-Sanz J, Muriel A, l Ron R, et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: A Multicenter Cohort Study. MedRxiv doi: https://doi.org/10.1101/2020.06.08.20125245
57) Petrak R, Skorodin N, Van Hise N, et al. Tocilizumab as a therapeutic agent for critically ill patients infected with SARS-CoV-2. MedRxiv doi: https://doi.org/10.1101/2020.06.05.20122622

58) Perrone P, Piccirillo MC, Ascierto PA, et al. Tocilizumab for patients with COVID-19 pneumonia. The TOCIVID-19 phase 2 trial. MedRXiv doi: https://doi.org/10.1101/2020.06.01.20119149

59) Garcia EM, Caballero VR, Albiach L, et al. Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection medRxiv doi: https://doi.org/10.1101/2020.06.05.20113738

59) Wadud N, Ahmed N, Shergil M, et al. Improved survival outcome in SARs-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration. MedRxiv doi: https://doi.org/10.1101/2020.05.13.20100081

60) Sanchez-Montalva A, Selares-Nadal J, Espinosa-Pereiro J, et al. Early outcomes of tocilizumab in adults hospitalized with severe COVID19. An initial report from the Vall dHebron COVID19 prospective cohort study. doi: https://doi.org/10.1101/2020.05.07.20094599

61) Ramaswamy M, Mannam P, Comer R, et al. Off-label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system: A case-control study medRxiv. doi: https://doi.org/10.1101/2020.05.14.20099234
62) Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol 2020; 2(8): e474-e484

63) Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol 2020; 2: e325–31

64) Cauchois R, Koubia M, Delarbre D, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Nat Acad Sci 2020; 117: 18951-18953

65) Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol 2020; 2: e393-e400

66) Kyriazopoulou E, Panagopoulos P, Metallidis S, et al. Anakinra to prevent respiratory failure in COVID-19. medRxiv preprint doi: https://doi.org/10.1101/2020.10.28.20217455; this version posted October 29, 2020.

67) Salvarani C, Dolci G, Massari M et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. JAMA Intern Med. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615
68) Rosas IO, Bräu N., Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia posted September 12, 2020.

medRxiv.https://doi.org/10.1101/2020.08.27.20183442doi:

69) Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. A randomized clinical trial Published Online: October 20, 2020. doi:10.1001/jamainternmed.2020.6820

70) Villar J, Ferrando C, Martínez D et al. Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267-276

71) Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX Randomized Clinical Trial. 2020 ;324(13):1307-1316.

72) RECOVERY Collaborative Group. Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. July 17, 2020 DOI: 10.1056/NEJMoa2021436

73) Salton F, Confalonieri P, Santus P, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. Open Forum Infectious Diseases, Volume 7, Issue 10, October 2020, ofaa421, https://doi.org/10.1093/ofid/ofaa421
74) Fadel R, Morrison AR, Vahia A, et al. Early short-course corticosteroids in hospitalized patients with COVID-1. Clinical Infectious Diseases 2020; ciaa601, https://doi.org/10.1093/cid/ciaa601

75) Villar J, Confalonieri, M, Pastore, SM, et al. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by Coronavirus Disease 2019. Crit Care Explor April 2020;2 :e0111

76) Marik PE, Kory P, Varon J, et al. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale, Expert Review of Anti-infective Therapy https://doi.org/10.1080/14787210.2020.1808462 published on line 18 aug 2020

77) Chroboczek T, Lacoste L, Wackenheim C, et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. MedRxiv: doi: https://doi.org/ 10.1101/2020.05.08.20094755

78) Jeronimo CMP, Farias MEL, BSc, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase iib, placebo-controlled trial. Clinical Infectious Diseases, ciaa1177, https://doi.org/10.1093/cid/ciaa1177

79) Dequin PF, Heming NMD, Mezian F, et al; Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19, A randomized clinical trial JAMA. 2020;324(13):1298-1306. doi:10.1001/jama.2020.16761
80) Derek C Angus DC, Derde L 3 4, Farah Al-Beidh F. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020 Oct 6;324(13):1317-1329. doi: 10.1001/jama.2020.17022

81) Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324(5):460-470.

82) Perotti C, Baldanti F, Bruno R, et al. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter interventional trial. Haematologica. 2020 Jul 23;haematol.2020.261784. doi: 10.3324/haematol.2020.261784

83) Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. MedRxiv September 1, 2020. https://doi.org/10.1101/2020.08.26.20182444doi:
84) Rogers R, Shehadeh F, Mylona E, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study medRxiv 2020.08.18.20177402; doi: https://doi.org/10.1101/2020.08.18.20177402

85) Joyner MJ, Klassen SA, Senefeld JW, et al. Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy. MedRxiv posted August 28, 2020.https://doi.org/10.1101/2020.07.29.20162917 doi: medRxiv pr

86) Joyner MJ, Bruno KA, Klassen SA, et al, Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients Mayo Clin Proc. 2020;95 (9):1888-1897

87) Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial) BMJ 2020;371:m3939 http://dx.doi.org/10.1136/bmj.m3939

88) Chen P, Nirula A, Heller B et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19 October 28, 2020, at NEJM.org. DOI: 10.1056/NEJMo2029849
89) Freedberg DE, Conigliaro J, Sobieszczyk ME, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Gastroenterology. 2020 May 22 doi: 10.1053/j.gastro.2020.05.053 [Epub ahead of print]

90) Deftereos SG, Giannopoulos G, Dimitrios A, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with Coronavirus Disease 2019. The GRECCO-19 randomized clinical trial. JAMA Network Open. 2020;3:e2013136.

91) Rocco PRM, Silva PL, Cruz FF, et al. Early use of nitazoxanide in mild Covid-19 disease: randomized, placebo-controlled trial medRxiv 2020.10.21.20217208; doi: https://doi.org/10.1101/2020.10.21.20217208

92) Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. A randomized clinical trial. JAMA. Published online November 12, 2020. doi:10.1001/jama.2020.22760

93) Behera P, Patro BK, Singh AK, et al. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study medRxiv 2020.10.29.20222661; doi: https://doi.org/10.1101/2020.10.29.20222661
94) Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. Archivos de Bronconeumología. 2020

95) Shouman W. https://ClinicalTrials.gov/show/NCT04422561 Results posted 27 Aug 20

96) Rajter JC, Sherman M, Fatteh N, et al. ICON (Ivermectin in COvid Nineteen) study: Use of ivermectin is associated with lower mortality in hospitalized patients with COVID19. medRxiv doi: https://doi.org/10.1101/2020.06.06.20124461

97) Shi L, Huang H, Lu X, et al. Treatment with human umbilical cord-derived mesenchymal stem cells for COVID-19 patients with lung damage: a randomised, double-blind, placebo-controlled phase 2 trial. medRxiv 2020.10.15.20213553; doi: https://doi.org/10.1101/2020.10.15.20213553

98) Folegatti PM, J Ewer KJ, Parvinder K Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 ;396(10249):467-478

99) Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 —preliminary report N Engl J Med. 2020 Jul 14;NEJMo2022483. doi: 10.1056/NEJMo2022483
100) Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo controlled, phase 2 trial. Lancet 2020; 395(10240);, P1845-1854, June 13, 2020

101) Keech C, Albert G, Cho I, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. New Engl J Med. DOI: 10.1056/NEJMoa2026920

102) Xia S, Duan K, Yuntao Zhang Y, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes. Interim analysis of 2 randomized clinical trials. JAMA 2020 ;e2015543.doi: 10.1001/jama.2020.15543

103) Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet. Published online September 4, 2020 https://doi.org/10.1016/S0140-6736(20)31866-31

104) Mulligan MJ, Lyke KE, Kitchin N, et al. Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: interim report. [published online ahead of print August 12, 2020] Nature 2020

105) Liu M, Thomadsen R, Yao S. Forecasting the spread of COVID-19 under different
reopening strategies. Nature Scientific Reports (In Press)

106) Institute for Health Metrics and Evaluation. COVID-19 projections. Covid.19.healthdata.org

107) Marik PE, Varon J, Kory P. Treatment of Covid-19 is critically phase specific. Crit Care Shock 2020;23:10-12

108) Wan Y, Shang J, Sun S, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. J Virol 2020;94:e02015-19.

109) Fatima K, Syed NI. Dengvaxia controversy: impact on vaccine hesitancy. J Glob Health. 2018; 8(2): 020312.

110) Edridge AWD, Kaczorowska J, Hoste ACR et al. Coronavirus protective immunity is short-lasting. medRxiv preprint doi: https://doi.org/10.1101/2020.05.11.20086439. this version posted June 16, 2020.

111) Flu Vaccination Coverage, United States, 2019–20 Influenza Season. FluVaxView webpage report posted online October 1, 2020

https://www.cdc.gov/flu/fluvoxview/coverage-1920estimates.htm
112) Zimmermann P, Nigel C. Coronavirus infections in children including COVID-19. An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. The Pediatric Infectious Disease Journal 2020;39: 355-368

113) Sepkowitz KA. AIDS-The first 20 years. N Engl J Med 2001; 344 (23):1764-1772

114) Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. Antiviral Res. 2010; 85(1): 1-18

115) Fauci AS. Preface: Evolving ethical issues over the course of the AIDS pandemic. Public Health Rev 34, 2 (2012)

116) Harris NS, Johnson AS, Huang YA, et al. Vital Signs: Status of human immunodeficiency virus testing, viral suppression, and HIV pre-exposure prophylaxis - United States, 2013-2018. MMWR Morb Mortal Wkly Rep. 2019; 68 (11):1117-1123
TABLE 1. PUBLISHED STUDIES AS OF DECEMBER 27, 2020. Each agent is listed along with the country originating the publication. We have listed studies with 100 or more subjects. The type of control procedure: RCT: Randomized controlled study  PLAC: Placebo, soc: standard of care which is variable depending on each location. AC: Active control: the control options are listed in parenthesis. OBS: retrospective observation study. LPV/R: lopanovir/ritonavir; HCQ: hydroxychloroquine; AZM: azithromycin; IFN: interferon; tocilizumab: TCZ. SEV: severe; CRIT: critical; MOD: moderate. W.H.O.: World Health Organization

| TREATMENT | LOCATION | TYPE OF CONTROL | NUMBER | SETTING | SEVERITY | RESULTS |
|-----------|----------|-----------------|--------|---------|----------|---------|
| Remdesivir<sup>8</sup> | China | RCTPLAC vs soc | 273 | HOSP | SEV | mortality in remdesivir group 14%, control 13% |
| Remdesivir<sup>9</sup> | U.S.A. | RCTPLAC | 1062 | HOSP | SEV,CRIT | 29 day mortality 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03) |
| Remdesivir<sup>10</sup> | U.S.A. | AC(5 day vs 10 day, no control) | 397 | HOSP | MOD,SEV | 10 day group had more severe disease, mortality 8% in 5 day group 11% in 10 day group |
| Remdesivir<sup>11</sup> | U.S.A. | AC(5 day vs 10 day, vs soc) | 596 | HOSP | MOD | Improved clinical status in 5 day group but not in 10 day group |
| Remdesivir<sup>12</sup> | W.H.O. | AC( 10 day, vs soc) | 5451 | HOSP | MOD,SEV | Mortality Remdesivir RR=0.95 (0.81-1.11, p=0.50 301/2743 active vs 303/2708 control |
| FVP\(^{14}\) | China | AC (umifenovir vs favipiravir) | 240 | HOSP | MOD, SEV | Clinical recovery rate 56% umifenovir vs 71% favipiravir time to fever reduction and cough shorter favipiravir |
|---|---|---|---|---|---|---|
| FVP\(^{15}\) | Japan | OBS (no control) | 1918 | HOSP | MOD, SEV, CRIT | Mortality 11.6% at one month |
| FVP\(^{17}\) | Russia | AC (FVP vs soc) | 196 | HOSP | MOD | By day 10 Clinical Improvement 27% FVP vs 15% soc , 98% neg PCR vs 79% |
| FVP\(^{18}\) | India | AC (FVP vs soc) | 150 | HOSP | MOD | median time to clinical cure of 3 days (95% CI: 3 days, 4 days) for FVP versus 5 days (95% CI: 4 days, 6 days) for control, P=0.030 |
| HCQ\(^{19}\) | France | OBS(hcq+azm, noncomparable control group) | 3737 | MIXED | MILD, MOD | 0.9% overall mortality, no sudden death, no cardiac arrhythmias |
| HCQ\(^{22}\) | China | RCT(hcq vs soc) | 150 | HOSP | MILD, MOD | No difference in viral clearance at 28 days |
| HCQ\(^{23}\) | U.S.A. | OBS(hcq vs no hcq) | 338 | HOSP | MOD, SEV | Mortality twice as high in patients chosen for HCQ treatment |
| HCQ\(^{24}\) | U.S.A. | OBS (hcq vs no hcq) | 1376 | HOSP | MOD, SEV | no significant association between HCQ use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32). |
HCQ treated patients were sicker with ppO2 223 vs 360 for controls still lower than controls after propensity score matching 223 vs 273

HCQ

| Study | Country | Comparator | Control | HOSP | MOD, SEV | Observation |
|-------|---------|------------|---------|------|---------|-------------|
| HCQ25 | U.S.A.  | OBS (hcq+azt vs hcq vs azt) | 1438    | HOSP | MOD, SEV | Overall in-hospital mortality was 20.3%, 25.7% hcq+azt, 19.9% hcq alone, neither drug 17.7%, cardiac arrest more likely with hcq+azt |
| HCQ26 | France  | OBS (hcq vs no hcq) | 181     | HOSP | MOD, SEV | no difference in mortality or need to transfer to ICU |
| HCQ27 | U.S.A.  | OBS (hcq vs hcq plus azm, azm) | 2512    | HOSP | MOD, SEV | 30-day unadjusted mortality for patients receiving hydroxychloroquine alone, azithromycin alone, the combination or neither drug was 25%, 20%, 18%, and 20%, |
| HCQ28 | U.S.A.  | OBS (hcq vs hcq plus azm, azm) | 2541    | HOSP | MOD, SEV | Overall mortality was 18.1% (95% CI:16.6%-19.7%); by treatment: hcq+azt, (20.1% [95% CI: 17.3%-23.0%]), hcq alone, (13.5% [95% CI: 11.6%-15.5%]), azt alone,(22.4% [95% CI: 16.0%-30.1%]), neither drug, (26.4% [95% CI: 22.2%-31.0%]). |
| HCQ29 | Brazil  | RCT (hcq, hcq+azm vs soc) | 504     | HOSP | SEV | Clinical status at 15 days no different with hcq, hcq+azm, soc |
| Medicine | Country | Study Design | Patients | Setting | Outcome |
|----------|---------|--------------|----------|---------|---------|
| HCQ      | Brazil  | RCT (azm vs soc) | 397      | HOSP    | SEV     | primary endpoint was not significantly different between the azithromycin and control groups (OR 1.36 [95% CI 0.94–1.97], p=0.11) |
| Chloroquine | Brazil | RCT (Chloroquine high dose to low dose) | 121      | HOSP    | MOD, SEV | No difference in viral clearance, higher mortality in high dose group |
| HCQ      | U.S.A.  | RCT (HCQ vs soc) | 479      | HOSP    | MOD, SEV | Mortality 28 days 10.4% HCQ, 10.6% soc |
| HCQ      | U.K.    | RCT (HCQ vs soc) | 1542     | HOSP    | MOD, SEV | Mortality 28-day mortality 26.8% hydroxychloroquine vs. 25% usual care; hazard ratio 1.09 [95% confidence interval 0.96–1.23]; p=0.18) (Mortality RR=1.19 (0.89–1.59, p=0.23; 104/947 HCQ vs 84/906 control) |
| HCQ      | W.H.O.  | AC (HCQ vs soc) | 1853     | HOSP    | MOD, SEV | Mortality RR=1.19 (0.89–1.59, p=0.23; 104/947 HCQ vs 84/906 control) |
| HCQ      | U.S.A.  | OBS (hcq+azm +zinc vs hzq +azm) | 932      | HOSP    | MOD, SEV | Reduction in mortality with addition of zinc OR 0.449, 95% CI 0.271–0.744. |
| HCQ      | U.S.A.  | RCTPLAC      | 821      | OUTPAT  | HEALTHY | No significant difference in incidence of subsequent COVID-19 infection (11.8% HCQ, 14.3% PLAC, p=0.35) |
| Study | Country | Design | N | Setting | Treatment | Outcome |
|-------|---------|--------|---|---------|-----------|---------|
| HCQ³⁶ | U.S.A. | RCTPLAC | 423 | OUTPAT | MILD | At 14 days, 24% (49 of 201) of participants receiving hydroxychloroquine had ongoing symptoms compared with 30% (59 of 194) receiving placebo (P = 0.21) |
| HCQ³⁷ | Spain | RCTPLAC | 293 | OUTPAT | MILD | no difference in viral load at 7 days after 6 days HCQ treatment nor risk of hospitalization compared to untreated patients |
| HCQ³⁸ | Spain | RCTPLAC | 2324 | OUTPAT | HEALTHY | no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54-1.46]), nor evidence of prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ) |
| HCQ³⁹ | Portugal | OBS(HCQ vs no HCQ) | 1293 | OUTPAT | HEALTHY | odds ratio of SARS-CoV-2 infection for chronic treatment with HCQ 0.51 (0.37-0.70). |
| HCQ⁴⁰ | U.S.A. | RCTPLAC | 132 | OUTPAT | HEALTHY | 2 month treatment with HCQ in hospital workers no significant difference in SARS-Cov-2 infection rate HCQ 6.3% vs placebo 6.6% |
| HCQ⁴¹ | Canada | RCTPLAC | 1483 | OUTPAT | HEALTHY | 3 month treatment with HCQ in hospital workers no significant difference in SARS-Cov-2 infection rate HCQ 0.27 events per person/year vs placebo 0.38% (p=0.18) |
| LPV/r⁴³ | China | RCT(soc) | 199 | HOSP | SEV | No differences in mortality, viral load; time to clinical improvement 1 day less in LPV/r group |
| Study | Country | Study Design | Study Pop. | Setting | Disease Severity | Results |
|-------|---------|--------------|------------|---------|-----------------|---------|
| LPV/r<sup>44</sup> | U.K. | RCT(soc) | 1596 | HOSP | MOD, SEV | no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58) |
| LPV/r<sup>12</sup> | W.H.O. | AC(LPV/r vs soc) | 2771 | HOSP | MOD, SEV | Mortality LPV/r (RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372) |
| LPV/r<sup>45</sup> | Hong Kong | AC (lpv/r+ribavirin vs lpv/r+ribavirin) | 127 | HOSP | MOD, SEV | Triple combination of interferon beta-1b, lpv/r, and ribavirin yielded more rapid viral clearance but attributable primarily to interferon |
| IFN- β-1a<sup>46</sup> | Cuba | OBS | 761 | HOSP | MIXED | Case fatality ratio 0.92 for interferon treated patients |
| IFN<sup>12</sup> | W.H.O. | AC (vs soc) | 4100 | HOSP | MOD, SEV | Mortality IFNRR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050) |
| IFN-α nasal drops<sup>50</sup> | China | OBS | 2944 | OUTPAT | HEALTHY | No cases of COVID-19 compared to historical control |
| IFN- β-1a(nebulized)<sup>51</sup> | U.K. | RCT(soc) | 101 | HOSP | MOD, SEV | OR for clinical improvement 2.32 (1.07–5.04) |
| Country | Treatment | Study Design | Sample Size | Setting | Outcomes |
|---------|-----------|--------------|-------------|---------|----------|
| U.S.A.  | OBS (TCZ vs soc) | 547 | HOSP | CRIT | 30 day unadjusted mortality with and without TCZ of 46% versus 56% |
| France  | Matched cohort (TCZ vs soc) | 168 | HOSP | SEV | TCZ was associated with a 45% reduction in hazard of death [hazard ratio 0.55 (95% CI 0.33, 0.90)] |
| Spain   | OBS | 1229 | HOSP | SEV | TCZ associated with a 51% reduction in composite of death and mechanical ventilation (HR)=0.49 (95% confidence interval (95%CI)=0.3-0.81), p-value=0.005) |
| U.S.A.  | OBS (TCZ early vs late treatment)) | 154 | HOSP | CRIT | Increased survival and avoidance mechanical ventilation with early treatment |
| Italy   | OBS | 1221 | HOSP | SEV | 15.6% mortality at 14 days, 20% at 30 days in TCZ treated patients |
| Spain   | OBS (TCZ vs soc) | 171 | HOSP | MOD, SEV | TCZ associated with decreased risk of ICU admission (10.3% vs. 27.6%, P=0.005) and need of invasive ventilation (0 vs 13.8%, P=0.001) |
| Treatment | Location | Study Design | N | Setting | Outcome 1 | Outcome 2 |
|-----------|----------|--------------|---|---------|-----------|-----------|
| TCZ       | Italy    | OBS (TCZ vs soc) | 544 | HOSP | SEV       | TCZ treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p=0·020). |
| Anakinra  | Greece   | OBS (vs soc)   | 130 | HOSP | SEV       | Incidence of severe respiratory failure 22% anakinra patients vs 59% soc., 30 day mortality 11.5% anakinra vs 22.3% soc. |
| TCZ       | U.S.A.   | RCTPLAC (TCZ vs soc) | 452 | HOSP | SEV, CRIT | No difference in mortality day 28 (19.7% TCZ, 19.4% PLAC) |
| TCZ       | France   | RCT (TCZ vs soc) | 130 | HOSP | SEV       | HR for mechanical ventilation or death at day 14 0.58 (90% CrI, 0.30 to 1.09). day 28 mortality 11.1% TCZ, 11.9% soc (adjusted HR, 0.92; 95% CI 0.33–2.53). |
| Dexamethasone | Brazil | RCT (soc) | 299 | HOSP | MOD, SEV | Dexamethasone increased ventilator free days from 4.0 to 6.6, no difference in 28 day mortality |
| Dexamethasone | U.K. | RCT (soc) | 6119 | HOSP | MOD, SEV | Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002 |
| Methylprednisolone | Italy | RCT (soc) | 173 | HOSP | SEV       | Methylprednisolone group had fewer deaths (6 vs. 21, adjusted HR = 0.29; 95% CI: 0.12–0.73) and more days off invasive MV (24.0 plus-or-minus sign 9.0 vs. 17.5 plus-or-minus sign 12.8; p=0.001) |
| Study | Country | Study Design | Sample Size | Setting | Outcome Measures |
|-------|---------|--------------|-------------|---------|------------------|
| Methylprednisolone<sup>7</sup> | U.S.A. | OBS(soc) | 213 | HOSP | SEV |
| Methylprednisolone<sup>7</sup> | Brazil | RCT(soc) | 393 | HOSP | MOD,SEV |
| Hydrocortisone<sup>79</sup> | France | RCT(soc) | 149 | HOSP | CRIT |
| Hydrocortisone<sup>80</sup> | U.S.A. | RCT(soc) | 403 | HOSP | SEV |
| Convalescent plasma<sup>81</sup> | China | RCT(soc) | 103 | HOSP | SEV.CRIT |
| Convalescent plasma<sup>82</sup> | U.S.A. | Matched cohort study | 241 | HOSP | SEV |

Early short course of methylprednisolone resulted in decrease need for ICU care, mechanical ventilation and mortality ((34.9% vs 54.3%, $P = .005$). Overall 28-day mortality was 76/199 (38.2%) in the placebo group vs 72/194 (37.1%) in group which received methylprednisolone short 5 day course ($P=0.629$).

Treatment failure in hydrocortisone group 42% vs 51% placebo.

90% probability of superiority of hydrocortisone in organ support free days. No mortality difference.

time to clinical improvement at 28 days was 4.9 days shorter (95% CI, −9.33 to −0.54 days) in convalescent plasma group (HR, 2.15 [95% CI, 1.07-4.32]; $P = .03$). No significant difference in critically ill patients. Mortality 28-day mortality (15.7% convalescent plasma vs 24.0% control ; $P = .30$).

No significant difference mortality or rate hospital discharge.
| Study                      | Country | Study Design | N     | Setting     | Outcomes                                                                 |
|---------------------------|---------|--------------|-------|-------------|--------------------------------------------------------------------------|
| Convalescent plasma^55    | U.S.A.  | OBS          | 3,082 | HOSP        | MOD, SEV adjusted 30-35 day mortality was 30% in patients treated with plasma with low antibody levels (IgG) 35 or more days after COVID-19 diagnosis. By contrast 30-day mortality was 20% in 353 patients treated within 3 days of diagnosis with plasma with high antibody levels. |
| Convalescent plasma^66    | U.S.A.  | OBS          | 21,987| HOSP        | MOD, SEV 7 day mortality 13%                                             |
| Convalescent plasma^86    | India   | RCT(soc)     | 464   | HOSP        | MOD, SEV Progression to severe disease or all cause mortality at 28 days after enrollment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54). |
| LY-CoV55^88               | U.S.A.  | RCT(soc)     | 452   | OUTPAT      | MILD, MOD 6.2% of patients receiving placebo had emergency room visit or hospitalization vs 1.6% patients who received antibody |
| Famotidine^89             | U.S.A.  | OBS(famotidine vs soc) | 1620  | HOSP        | MOD, SEV HR for famotidine for death or intubation 0.43, 95% CI (0.21-0.88) |
| Nitazoxanide^90           | Brazil  | RCTPLAC(Nitazoxanide vs plac) | 392   | OUTPAT      | MILD Art one week, 78% complete resolution symptoms in the nitazoxanide arm and 57% in the placebo arm (p=0.048). viral clearance in 29.9% of patients in the nitazoxanide arm versus 18.2% in the placebo arm (p=0.009). |
| Drug                  | Country   | Study Type (Drug vs Comparator) | Number | Setting | Disease | Findings |
|-----------------------|-----------|---------------------------------|--------|---------|---------|----------|
| Fluvoxamine           | U.S.A.    | RCT (fluvoxamine vs soc)        | 152    | OUTPAT  | MILD, MOD | Clinical deterioration in 0 patients on fluvoxamine, 8.7% placebo (p<0.009) |
| Ivermectin            | U.S.A.    | OBS (ivermectin vs soc)         | 280    | HOSP    | MOD, SEV | Lower mortality in the ivermectin group (25.2% versus 15.0%, OR 0.52, 95% CI 0.29-0.96, P=.03) |
| Ivermectin            | India     | Case Control (Ivermectin vs placebo) | 115    | OUTPAT  | HEALTHY | Two doses of ivermectin yielded 73% reduction in COVID-9 cases |
| Ivermectin            | Bangladesh| OBS (ivermectin vs soc)         | 248    | HOSP    | MOD, SEV | Mortality 0.9% ivermectin vs 6.8% control |
| Ivermectin            | Egypt     | RCT (ivermectin vs soc)         | 304    | OUTPAT  | HEALTHY | 7.4% developed COVID symptoms ivermectin vs 58.4% control |
| Mesenchymal Stem Cells | China     | RCTPLAC (Ivermectin vs placebo) | 101    | HOSP    | SEV WITH LUNG DAMAGE | Lesion volume decreased compared to placebo (p<0.05) |
| ChAdOx1-nCoV19        | U.K.      | RCT (plac)                      | 1077   | OUTPAT  | HEALTHY | 100% spike protein neutralising antibody, spike specific T cell responses |
| mRNA1273              | U.S.A.    | RCT (plac)                      | 45     | OUTPAT  | HEALTHY | High neutralising antibody titers, positive Th1-CD4 response |
| Ad5 vectored Covid Vaccine | China     | RCT (plac)                      | 603    | OUTPAT  | HEALTHY | Significant neutralizing antibody titers and positive T cell response |
| Vaccine                          | Country    | Study Design | Patients | Status   | Outcome                                                                 |
|---------------------------------|------------|--------------|----------|----------|-------------------------------------------------------------------------|
| NVX-Cov2373<sup>101</sup>       | Australia  | RCT(plac)    | 134      | OUTPAT   | HEALTHY Significant neutralizing antibody titers and positive T cell response |
| Coronavac<sup>102</sup>         | China      | RCT(plac)    | 330      | OUTPAT   | HEALTHY Significant neutralizing antibody titers and positive T cell response |
| Ad5 and Ad26 vectored Covid Vaccines<sup>103</sup> | Russia    | OBS         | 76       | OUTPAT   | HEALTHY Significant neutralizing antibody titers and positive T cell response |
| BTN162b1 and b2<sup>104</sup>   | U.S.A.     | RCT(plac)    | 195      | OUTPAT   | HEALTHY high titer, broad serum neutralizing responses, TH1 phenotype CD4+ T helper cell responses, and strong interferon γ (IFNγ) and interleukin-2 (IL-2) producing CD8+ cytotoxic T-cell responses |
Figure 1: THE PHASES OF COVID-19 INFECTION. Asymptomatic viremia typically lasts for 5 days followed by symptoms of an upper respiratory infection. The immune response takes hold over the next week. Pneumonic infiltrates begin to appear. In patients destined for severe infection, a hyperinflammatory reaction takes hold, leading to worsening of pulmonary symptoms, hypoxia, and potentially acute respiratory distress syndrome.
| Trial Registration | Country  | Projected Date | Subjects | Agents Studied                                                                 | Number |
|--------------------|----------|----------------|----------|--------------------------------------------------------------------------------|--------|
| CHICTR2000030946   | China    | 2020-Apr       | HOSP     | Anticoagulants, Other                                                            | 120    |
| CHICTR2000029898   | China    | 2020-Apr       | HOSP     | HCQ                                                                              | 100    |
| NCT04282902        | China    | 2020-Apr       | HOSP     | Pirfenidone                                                                     | 294    |
| CHICTR2000030179   | China    | 2020-Apr       | HOSP     | Plasma based therapy, SOC                                                        | 100    |
| CHICTR2000030545   | China    | 2020-Apr       | HOSP     | SO, Herbal tea                                                                   | 300    |
| NCT04480593        | Brazil   | 2020-Aug       | HOSP     | Alternative therapy, SOC                                                         | 120    |
| NCT04335552        | United States | 2020-Aug   | HOSP     | AZM, HCQ, SOC                                                                   | 500    |
| NCT04355637        | Spain    | 2020-Aug       | HOSP     | Corticosteroids, SOC                                                             | 300    |
| NCT04349592        | Qatar    | 2020-Aug       | HOSP     | HCQ, HCQ + AZM, SOC                                                             | 456    |
| NCT04347031        | Russia   | 2020-Aug       | HOSP     | HCQ, Other, TCZ +AZM                                                            | 320    |
| NCT04394442        | Saudi Arabia | 2020-Aug   | HOSP     | HCQ, SOC                                                                        | 200    |
| NCT04420247        | Brazil   | 2020-Aug       | HOSP     | HCQ, SOC                                                                        | 100    |
| NCT04476888        | Pakistan | 2020-Aug       | HOSP     | Plasma based therapy, SOC                                                        | 100    |
| NCT04349098        | United States | 2020-Aug   | HOSP     | Selinexor, SOC                                                                  | 230    |
| NCT04326426        | United States | 2020-Aug   | HOSP     | Tradipitant (neurokinin 1 inhibitor), SOC                                        | 300    |
| NCT04445272        | Spain    | 2020-Aug       | HOSP     | TCZ                                                                             | 500    |
| NCT04311697        | United States | 2020-Aug   | HOSP     | Aviptadil Inhaled solution, SOC                                                  | 144    |
| NCT04381858        | Mexico   | 2020-Aug       | HOSP     | Igs, Plasma based therapy                                                        | 500    |
| NCT04325906        | United States | 2020-Aug   | HOSP     | Non-invasive respiratory support, Positioning + Non-invasive respiratory support  | 346    |
| NCT04394377        | Brazil   | 2020-Dec       | HOSP     | Anticoagulants                                                                  | 600    |
| NCT043451724       | Austria  | 2020-Dec       | HOSP     | Anticoagulants, HCQ, LPV/r, mAb, RAS blockade, SOC                              | 500    |
| NCT04452565        | United States | 2020-Dec   | HOSP     | Antiretroviral + Dexamethasone, Other, Other + Antiretroviral, Other + Dexamethasone | 525    |
| NCT04396106        | United States | 2020-Dec   | HOSP     | AT-527 RNA polymerase inhibitor                                                 | 190    |
| NCT04365699        | United States | 2020-Dec   | HOSP     | AT001, SOC                                                                      | 500    |
| NCT04321096        | Denmark  | 2020-Dec       | HOSP     | Camostat, SOC                                                                   | 580    |
| NCT04321531        | Spain    | 2020-Dec       | HOSP     | Cyclosporine, SOC                                                               | 120    |
| NCT04397718        | United States | 2020-Dec   | HOSP     | Hormone therapy, SOC                                                            | 198    |
| NCT04421027        | United States | 2020-Dec   | HOSP     | JAKi, SOC                                                                        | 600    |
| NCT04469114 | Israel | 2020-Dec | HOSP | JAKi, SOC | 260
| NCT04347239 | United States | 2020-Dec | HOSP | Leronlimab, SOC | 390
| NCT04376684 | United States | 2020-Dec | HOSP | mAb, SOC | 800
| NCT04401202 | Saudi Arabia | 2020-Dec | HOSP | Nigella sativa, SOC | 200
| NCT04432298 | United States | 2020-Dec | HOSP | pamrevlumab (Ab to connective tissue growth factor), SOC | 130
| NCT04433546 | United States | 2020-Dec | HOSP | pemziviptadil, SOC | 210
| NCT04376684 | United States | 2020-Dec | HOSP | Plasma based therapy | 100
| NCT04400058 | United States | 2020-Dec | HOSP | Plasma based therapy, SOC | 208
| NCT04391140 | Spain | 2020-Dec | HOSP | Positioning + Respiratory support, Respiratory support | 248
| NCT04424797 | United States | 2020-Dec | HOSP | Positioning | 100
| NCT04424797 | United States | 2020-Dec | HOSP | TCZ | 106
| NCT04317092 | Italy | 2020-Dec | HOSP | Plasma based therapy, SOC | 106
| NCT04443910 | Germany | 2020-Dec | HOSP | Plasma based therapy, SOC | 106
| NCT0446389 | United States | 2020-Dec | HOSP | Anticoagulants | 186
| NCT044730 | France | 2020-Dec | HOSP | Dexamethasone with or without respiratory support, SOC | 550
| NCT04480424 | United States | 2020-Dec | HOSP | Ivlg, SOC | 100
| NCT0443881 | Spain | 2020-Dec | HOSP | Anakinra, SOC | 180
| NCT04485429 | Brazil | 2020-Dec | HOSP | Anticoagulants, Anticoagulants + Corticosteroids, Corticosteroids, | 268
| NCT0446670 | Brazil | 2020-Dec | HOSP | Anticoagulants, Antihypertensive | 310
| NCT04435063 | Argentina | 2020-Dec | HOSP | FX12 antibody, SOC | 124
| NCT04336462 | China | 2020-Feb | HOSP | Plasma based therapy | 200
| CHICTR2000032367 | China | 2020-Jul | HOSP | Hydrogen, oxygen, SOC | 100
| NCT04535063 | Argentina | 2020-Dec | HOSP | Plasma based therapy | 100
| NCT0449509 | United States | 2020-Dec | HOSP | Plasma based therapy, SOC | 426
| NCT0435523 | Spain | 2020-Jul | HOSP | Plasma based therapy, SOC | 278
| NCT04468646 | Pakistan | 2020-Jul | HOSP | Neurokinin 1 receptor agonist, SOC | 100
| CHICTR2000030333 | China | 2020-Jul | HOSP | Pirfenidone, SOC | 292
| NCT04459325 | Russia | 2020-Jul | HOSP | Dornase, alfa | 100
| NCT04322344 | Italy | 2020-Jun | HOSP | Alternative therapy, SOC | 120
| Study ID          | Country     | Start Date | Study Type | Interventions                                                                 |
|------------------|-------------|------------|------------|-------------------------------------------------------------------------------|
| NCT04305106      | China       | 2020-Jun   | HOSP       | Bevacizumab, SOC                                                              |
| NCT04375202      | Italy       | 2020-Jun   | HOSP       | Colchicine, SOC                                                               |
| NCT04347980      | France      | 2020-Jun   | HOSP       | Dexamethasone + HCQ, HCQ                                                      |
| CHICTR2000029777 | China       | 2020-Jun   | HOSP       | SOC, Herbal tea                                                               |
| CHICTR2000029781 | China       | 2020-Jun   | HOSP       | SOC, Herbal tea                                                               |
| CHICTR2000034796 | China       | 2020-Mar   | HOSP       | Anticoagulants, SOC                                                           |
| NCT04329195      | France      | 2020-May   | HOSP       | Antihypertensive                                                             |
| NCT04329650      | Spain       | 2020-May   | HOSP       | Corticosteroids, Siltuximab                                                   |
| CHICTR2000030894 | China       | 2020-May   | HOSP       | FPV, FPV + TCZ, TCZ                                                          |
| CHICTR2000029603 | China       | 2020-May   | HOSP       | LPV/r, ASC09/r                                                                |
| CHICTR2000030001 | China       | 2020-May   | HOSP       | LPV/r, Emcetabrine/r, SOC                                                     |
| CHICTR2000029763 | China       | 2020-May   | HOSP       | SOC, Heral Tea                                                               |
| CHICTR2000029755 | China       | 2020-May   | HOSP       | SOC, Herbal tea                                                              |
| CHICTR2000029765 | China       | 2020-May   | HOSP       | SOC, TCZ                                                                     |
| CHICTR2000030779 | China       | 2020-May   | HOSP       | Fulinastatin, SOC                                                             |
| NCT04310228      | China       | 2020-May   | HOSP       | FPV, FPV + TCZ, TCZ                                                          |
| NCT04346199      | Argentina   | 2020-Nov   | HOSP       | Acalabrutinib, SOC                                                            |
| NCT0444700       | Brazil      | 2020-Nov   | HOSP       | Anticoagulants, SOC                                                           |
| NCT04362085      | Canada      | 2020-Nov   | HOSP       | Anticoagulants, SOC                                                           |
| NCT04344288      | France      | 2020-Nov   | HOSP       | Corticosteroids, SOC                                                         |
| NCT04382053      | Brazil      | 2020-Nov   | HOSP       | DFV890, SOC                                                                  |
| NCT04358081      | United States| 2020-Nov  | HOSP       | HCQ, HCQ + AZM, SOC                                                         |
| NCT04362137      | United States| 2020-Nov  | HOSP       | JAKi, SOC                                                                    |
| NCT04511819      | United States| 2020-Nov  | HOSP       | Losmapimod, SOC                                                              |
| NCT04448756      | United States| 2020-Nov  | HOSP       | M5049 (toll like receptor inhibitor), Other                                  |
| NCT04441385      | Spain       | 2020-Nov   | HOSP       | Maraviroc, SOC                                                               |
| NCT04463420      | Iran        | 2020-Nov   | HOSP       | PHR160 asal spray+ HCO + NSAIDs + AZM                                       |
| NCT04388410      | Mexico      | 2020-Nov   | HOSP       | Plasma based therapy, SOC                                                     |
| NCT04495101      | Spain       | 2020-Nov   | HOSP       | prolastatin (proteinase inhibitor), SOC                                       |
| NCT0449718       | Brazil      | 2020-Nov   | HOSP       | SOC, Vitamin D                                                               |
| NCT04386850      | Iran        | 2020-Nov   | HOSP       | Positioning                                                                  |
| NCT04389400      | Denmark     | 2020-Nov   | HOSP       | Plant polyphenols                                                            |
| NCT04400890      | United States| 2020-Nov  | HOSP       | Positioning, SOC                                                             |
| NCT04477655      | Mexico      | 2020-Nov   | HOSP       | Anticoagulants                                                               |
| NCT04427098      | Italy       | 2020-Oct   | HOSP       | Anticoagulants                                                               |
| NCT04530578      | Argentina   | 2020-Oct   | HOSP       | Anticoagulants                                                               |
| NCT Number      | Country     | Start Date | Intervention                                                                 |
|-----------------|-------------|------------|------------------------------------------------------------------------------|
| NCT04486508    | Iran        | 2020-Oct   | Anticoagulants, SOC, Statins                                                  |
| NCT04470622    | United States | 2020-Oct  | Aprepitant (antiemetic), SOC                                                 |
| NCT04340557    | United States | 2020-Oct  | ARBs, SOC                                                                    |
| NCT04364893    | Brazil      | 2020-Oct   | ARBs + ACEi, SOC                                                             |
| NCT04350320    | Spain       | 2020-Oct   | Colchicine, SOC                                                              |
| NCT04322396    | Denmark     | 2020-Oct   | HCQ + AZM, SOC                                                               |
| NCT04348656    | United States | 2020-Oct  | Plasma based therapy, SOC                                                    |
| NCT04385043    | Italy       | 2020-Oct   | Plasma based therapy, SOC                                                    |
| NCT04395144    | Canada      | 2020-Oct   | Positioning, SOC                                                             |
| NCT04335071    | Switzerland | 2020-Oct   | SOC, TCZ                                                                      |
| NCT04385836    | Saudi Arabia | 2020-Sep  | alpha1 antitrypsin, SOC                                                      |
| NCT04341116    | United States | 2020-Sep  | anti GM-CSF, SOC                                                             |
| NCT04335136    | Austria     | 2020-Sep   | Antihypertensive, SOC                                                        |
| NCT04386616    | United States | 2020-Sep  | astegolimab, SOC                                                             |
| NCT04452435    | India       | 2020-Sep   | C21, SOC                                                                     |
| NCT04451174    | Chile       | 2020-Sep   | Corticosteroids, SOC                                                         |
| NCT04332094    | Spain       | 2020-Sep   | HCQ, AZM, TCZ + AZM + HCQ                                                    |
| NCT04370262    | United States | 2020-Sep  | HCQ, HCQ + LPV/r, LPV/r, SOC                                                  |
| NCT04351152    | United States | 2020-Sep  | Lenzilumab, SOC                                                              |
| NCT04334629    | United Kingdom | 2020-Sep | NSAIDs, SOC                                                                  |
| NCT04374526    | Italy       | 2020-Sep   | Plasma based therapy, SOC                                                    |
| CHICTR2000030522 | China    | 2020-Sep   | SOC, Herbal tea                                                              |
| NCT04379271    | Bulgaria    | 2020-Sep   | vidofludimus (pyrimidine synthesis inhibitor), SC                           |
| NCT04377620    | United States | 2020-Sep  | JAKi, SOC                                                                    |
| NCT04445935    | Qatar       | 2020-Sep   | Anticoagulants, SOC                                                          |
| NCT04359277    | United States | 2021-Apr  | Anticoagulants                                                               |
| NCT04360824    | United States | 2021-Apr  | Anticoagulants                                                               |
| NCT04360824    | United States | 2021-Apr  | Anticoagulants                                                               |
| NCT04312009    | United States | 2021-Apr  | ARBs                                                                        |
| NCT04381377    | Russia      | 2021-Apr   | Azoximer bromide, SOC                                                        |
| NCT04367168    | Mexico      | 2021-Apr   | Colchicine, SOC                                                              |
| IRCT20200517047485N1 | Iran   | 2021-Apr   | HCQ + Atazanavir/ritonavir, HCQ + LPV/r                                      |
| NCT04328493    | Vietnam     | 2021-Apr   | HCQ, SOC                                                                    |
| NCT04328493    | Vietnam     | 2021-Apr   | HCQ, SOC                                                                    |
| NCT Number   | Country       | Start Date | Intervention                                      | Study Type | Patients |
|--------------|---------------|------------|--------------------------------------------------|------------|----------|
| NCT04320056 | Canada        | 2021-Apr   | Non-invasive respiratory support, SOC            | HOSP       | 216      |
| NCT04344431 | France        | 2021-Apr   | Non-invasive respiratory support, SOC            | HOSP       | 100      |
| NCT04362176 | United States | 2021-Apr   | Plasma based therapy, SOC                        | HOSP       | 500      |
| NCT04359797 | United States | 2021-Apr   | Positioning                                     | HOSP       | 300      |
| NCT04346615 | United States | 2021-Apr   | Zavegepant (CGRP agonist), SOC                   | HOSP       | 120      |
| NCT04352751 | Pakistan      | 2021-Apr   | Plasma based therapy                            | HOSP       | 2000     |
| NCT04344431 | France        | 2021-Apr   | Non-invasive respiratory support, SOC            | HOSP       | 100      |
| NCT04351358 | United States | 2021-Aug   | Plasma based therapy                            | HOSP       | 100      |
| NCT04345692 | United States | 2021-Dec   | HCQ, SOC                                        | HOSP       | 350      |
| CHICTR2000029739 | China | 2021-Dec   | RECOVERY TRIAL Conv plasma vs TCZ vs Monoclonal Abs | HOSP     | 15000    |
| NCT043489710 | United States | 2021-Aug   | Plasma based therapy                            | HOSP       | 100      |
| NCT04355143 | United States | 2021-Apr   | Colchicine, SOC                                 | HOSP       | 150      |
| NCT04387760 | Bahrain       | 2021-Apr   | FPV, HCQ, SOC                                   | HOSP       | 150      |
| NCT04381936 | United Kingdom | 2021-Dec  | RECOVERY TRIAL Conv plasma vs TCZ vs Monoclonal Abs | HOSP   | 200      |
| NCT04363814 | Dominican Republic | 2021-Jul  | BAKTEC-R bacterial identification, SOC           | HOSP       | 100      |
| NCT04513158 | United States | 2021-Aug   | Plasma based therapy                            | HOSP       | 100      |
| NCT04387760 | Bahrain       | 2021-Apr   | FPV, HCQ, SOC                                   | HOSP       | 150      |
| NCT04339816 | Czechia       | 2021-Dec   | Antibody to GM-CSF                              | HOSP       | 573      |
| NCT04345692 | United States | 2021-Dec   | HCQ, HCQ + AZM                                  | HOSP       | 186      |
| NCT04379933 | Brazil        | 2021-Feb   | JAKi, SOC                                       | HOSP       | 200      |
| NCT043393246 | United Kingdom | 2021-Feb  | Other, SGLT2 + Other, SOC                       | HOSP       | 1407     |
| CHICTR2000029757 | China | 2021-Feb   | Plasma based therapy, SOC                       | HOSP       | 200      |
| NCT04348383 | Spain         | 2021-Jan   | Antithrombotics, SOC                            | HOSP       | 120      |
| NCT043390594 | Senegal       | 2021-Feb   | Antibody to GM-CSF                              | HOSP       | 573      |
| NCT04379933 | Brazil        | 2021-Feb   | JAKi, SOC                                       | HOSP       | 200      |
| NCT04460183 | United Kingdom | 2021-Jan  | Non-invasive respiratory support, SOC            | HOSP       | 300      |
| CHICTR2000029806 | China | 2021-Jan   | Plasma based therapy, SOC                       | HOSP       | 200      |
| NCT04349071 | United States | 2021-Jan   | PTC299 (DDODH inhibitor), SOC                   | HOSP       | 380      |
| NCT04363814 | Dominican Republic | 2021-Jul  | BAKTEC-R bacterial identification, SOC           | HOSP       | 100      |
| NCT04514631 | Switzerland   | 2021-Jun   | Conestat alfa (C1esterase inhibitor), SOC       | HOSP       | 120      |
| NCT04345289 | Denmark       | 2021-Jun   | Conv Plasma                                     | HOSP       | 1100     |
| NCT04322722 | United States | 2021-Jun   | Plasma based therapy                            | HOSP       | 500      |
| NCT Number   | Country            | Start-Month | Study Type | Intervention                                                                 |
|-------------|--------------------|-------------|------------|------------------------------------------------------------------------------|
| NCT04418518 | United States      | 2021-Jun    | HOSP       | Plasma-based therapy, SOC                                                    |
| NCT04364763 | United States      | 2021-Jun    | HOSP       | RBT-9 (antiviral), SOC                                                       |
| NCT04322773 | Denmark            | 2021-Jun    | HOSP       | Sarilumab, SOC, TCZ                                                         |
| NCT04323514 | Italy              | 2021-Mar    | HOSP       | Axcorbiac Acid                                                              |
| IRCT20170731035423N2 | Iran | 2021-Mar | HOSP | BCC1 and Hep S, SOC                                                          |
| NCT04420299 | Spain              | 2021-Mar    | HOSP       | Bemiparin (low molecular wt heparin), SOC                                   |
| NCT04351763 | Poland             | 2021-Mar    | HOSP       | CCB, Other, SOC                                                             |
| NCT04476979 | France             | 2021-Mar    | HOSP       | Corticosteroids, TCZ + Corticosteroids                                       |
| NCT04373733 | United Kingdom     | 2021-Mar    | HOSP       | FPV, HCQ + AZM + Zinc, SOC                                                   |
| NCT04422221 | Germany            | 2021-Mar    | HOSP       | HCQ, SOC                                                                    |
| IRCT20170922036314N4 | Iran | 2021-Mar | HOSP | Psychological therapy, SOC                                                   |
| NCT04380961 | United States      | 2021-Mar    | HOSP       | sirukamab (IL6 inhibitor), SOC                                               |
| NCT04306393 | United States      | 2021-Mar    | HOSP       | Non-invasive respiratory support, SOC                                        |
| NCT04306393 | United States      | 2021-Mar    | HOSP       | Non-invasive respiratory support, SOC                                        |
| NCT04376034 | United States      | 2021-Mar    | HOSP       | Plasma based therapy, SOC                                                   |
| NCT04366050 | United States      | 2021-May    | HOSP       | ACEi, SOC                                                                   |
| NCT04379492 | United States      | 2021-May    | HOSP       | HCQ, SOC                                                                    |
| NCT04334420 | Netherlands        | 2021-May    | HOSP       | IFN, SOC                                                                    |
| NCT04089020 | United Kingdom     | 2021-May    | HOSP       | JAKi, mAb, SOC                                                              |
| NCT04365985 | United States      | 2021-May    | HOSP       | Opiate antagonists, Opiate antagonists + Anesthetic, SOC                    |
| NCT04516915 | United Kingdom     | 2021-May    | HOSP       | Oseltamivir, vidofludimus + Oseltamivir                                     |
| IRCT20200501047258N1 | Iran | 2021-May | HOSP | Plasma based therapy, SOC                                                   |
| NCT04374593 | Spain              | 2021-May    | HOSP       | Plasma based therapy, SOC                                                   |
| NCT04367077 | United States      | 2021-Sep    | HOSP       | SOC, Stem cells                                                             |
| NCT04415086 | Brazil             | 2022-Apr    | HOSP       | Plasma-based therapy, SOC                                                   |
| NCT04387071 | United States      | 2022-Aug    | HOSP       | Vadadustat(hypoxia inducible factor), SOC                                   |
| NCT04321993 | Canada             | 2022-Feb    | HOSP       | HCQ, JAKi, LPV/r, Sarilumab                                                 |
| NCT04394416 | United States      | 2022-Jun    | HOSP       | Imatinib, SOC                                                               |
| NCT04330690 | Canada             | 2022-Mar    | HOSP       | LPV/r, SOC                                                                  |
| NCT04354831 | United States      | 2022-May    | HOSP       | Plasma based therapy                                                        |
| NCT04412486 | United States      | 2022-May    | HOSP       | Plasma based therapy                                                        |
| NCT04470544 | United States      | 2022-Sep    | HOSP       | Camostat, SOC                                                               |
| NCT04364737 | United States      | 2023-Jan    | HOSP       | Plasma based therapy, SOC                                                   |
| NCT04276896 | China              | 2023-Jul    | HOSP       | LV-SMENP-DC Vaccine                                                         |
| NCT04415060 | Canada             | 2023-Jun    | HOSP       | Anesthetic, SOC                                                             |
| Clinical Trial ID   | Country       | Start Date | Phase | Interventions                                                                 | Participants |
|--------------------|---------------|------------|-------|-------------------------------------------------------------------------------|--------------|
| NCT04315948        | Austria       | 2023-Mar   | HOSP  | HCQ, LPV/r, LPV/r + IFN, Remdesivir, SOC                                       | 3100         |
| CTRI/2020/05/025434| Kazakhstan    | NA         | HOSP  | Alternative therapy                                                           | 200          |
| CTRI/2020/06/025977| India         | NA         | HOSP  | Alternative therapy, SOC                                                       | 135          |
| CTRI/2020/06/025590| India         | NA         | HOSP  | Alternative therapy, SOC                                                       | 120          |
| CTRI/2020/04/024883| India         | NA         | HOSP  | Alternative therapy, SOC                                                       | 112          |
| NCT04347226        | United States | NA         | HOSP  | anti-IL8, SOC                                                                 | 138          |
| ACTRN126200000517976| Australia    | NA         | HOSP  | Anticoagulants, SOC                                                           | 206          |
| NCT04493359        | Brazil        | NA         | HOSP  | Antihypertensive                                                              | 240          |
| NCT04328012        | United States | NA         | HOSP  | ARBs, HCQ, LPV/r, SOC                                                        | 4000         |
| ISRCTN48734830     | Sweden        | NA         | HOSP  | ARBs, SOC                                                                     | 750          |
| NCT04335786        | Netherlands   | NA         | HOSP  | ARBs, SOC                                                                     | 651          |
| CTRI/2020/05/025319| India         | NA         | HOSP  | ARBs, SOC                                                                     | 186          |
| CTRI/2020/05/025271| India         | NA         | HOSP  | BCG, SOC                                                                      | 480          |
| NCT0434460         | United States | NA         | HOSP  | BLD2660 (protease inhibitor), SOC                                             | 120          |
| CTRI/2020/06/026192| India         | NA         | HOSP  | C21, SOC                                                                      | 100          |
| NCT04362813        | United States | NA         | HOSP  | Canakinumab, SOC                                                              | 450          |
| NCT04328480        | Argentina     | NA         | HOSP  | Colchicine, SOC                                                               | 2500         |
| NCT04381364        | Sweden        | NA         | HOSP  | Corticosteroids, SOC                                                          | 446          |
| NCT04331054        | France        | NA         | HOSP  | Corticosteroids, SOC                                                          | 436          |
| NCT04323592        | Italy         | NA         | HOSP  | Corticosteroids, SOC                                                          | 104          |
| NCT04345614        | United States | NA         | HOSP  | CRAC channel inhibitor, SOC                                                   | 400          |
| NCT04395105        | Argentina     | NA         | HOSP  | Dexamethasone, SOC                                                            | 284          |
| NCT04424901        | United States | NA         | HOSP  | Dipyridamole, SOC                                                             | 100          |
| 2020-001643-13     | United Kingdom| NA         | HOSP  | DPP1 inhibitor, SOC                                                           | 300          |
| ISRCTN30564012     | United Kingdom| NA         | HOSP  | DPP1 inhibitor, SOC                                                           | 300          |
| NCT04494984        | Argentina     | NA         | HOSP  | Equine hyperimmune serum, SOC                                                 | 242          |
| JPRN-JRCTS031190226| Japan         | NA         | HOSP  | FPV                                                                          | 100          |
| NCT04411433        | Turkey        | NA         | HOSP  | FPV, FPV + AZM, HCQ, HCQ + AZM, HCQ + FPV                                   | 1000         |
| CTRI/2020/06/025957| India         | NA         | HOSP  | FPV, FPV + Umifenovir                                                        | 158          |
| 2020-001904-41     | United Kingdom| NA         | HOSP  | FPV, SOC                                                                      | 302          |
| Study ID               | Country                  | Phase | Intervention                                                                 | Participants |
|-----------------------|--------------------------|-------|------------------------------------------------------------------------------|--------------|
| CTRI/2020/06/025704   | India                    | HOSP  | HCQ + AZM, HCQ + Other + AZM                                                | 120          |
| NCT04355052           | Israel                   | HOSP  | HCQ + AZM, HCQ + Other, SOC                                                  | 250          |
| NCT04392973           | Saudi Arabia             | HOSP  | HCQ + FPV, SOC                                                               | 520          |
| NCT04346147           | Spain                    | HOSP  | HCQ + Imatinib, HCQ + JAKi, HCQ + LPV/r                                     | 165          |
| 2020-002035-30        | Italy                    | HOSP  | HCQ, HCQ + JAKi                                                              | 116          |
| 2020-000936-23        | Austria                  | HOSP  | HCQ, LPV/r, Remdesivir                                                      | 3100         |
| PACTR202004801273802  | Nigeria                  | HOSP  | HCQ, SOC                                                                     | 800          |
| ISRCTN88057279        | United Kingdom           | HOSP  | HCQ, SOC                                                                     | 500          |
| NCT04459676           | Brazil                   | HOSP  | heptocyte growth factor, SOC                                               | 100          |
| NCT04382924           | United States            | HOSP  | Ifenprodil, SOC                                                             | 682          |
| 2020-001023-14        | United Kingdom           | HOSP  | IFN, SOC                                                                      | 400          |
| NL8491                | Netherlands              | HOSP  | imatinib, SOC                                                                | 386          |
| CTRI/2020/04/024806   | India                    | HOSP  | Imatinib, SOC                                                                | 100          |
| 2020-001750-22        | United Kingdom           | HOSP  | Immunomodulators, JAKi, SOC                                                 | 186          |
| NCT04402866           | United Kingdom           | HOSP  | JAK1, SOC                                                                    | 159          |
| NCT04373044           | United States            | HOSP  | JAKi, HCQ, SOC                                                               | 144          |
| ISRCTN11188345        | United Kingdom           | HOSP  | JAKi, mAb, SOC                                                               | 375          |
| NCT04404361           | United States            | HOSP  | JAKi, SOC                                                                    | 358          |
| 2020-001807-18        | Finland                  | HOSP  | JAKi, SOC                                                                    | 159          |
| 2020-001759-42        | Argentina                | HOSP  | mAb, SOC                                                                     | 800          |
| NCT04382651           | United States            | HOSP  | MAS825, SOC                                                                  | 120          |
| NCT04374032           | Bosnia & Herzegovina     | HOSP  | metenkefalin + tridecactide, SOC                                            | 120          |
| ISRCTN40580903        | United Kingdom           | HOSP  | Mylotarg, Infliximab, Namilumab, SOC                                        | 588          |
| 2020-001236-10        | Netherlands              | HOSP  | NA                                                                           | 304          |
| NCT04395807           | Sweden                   | HOSP  | Non-invasive respiratory support                                           | 120          |
| NCT04467840           | Israel                   | HOSP  | opaganib (sphingosine kinase), SOC                                          | 270          |
| 2020-001805-21        | United Kingdom           | HOSP  | Oseltamivir, Oseltamivir + Other                                           | 120          |
| 2020-002229-27        | United Kingdom           | HOSP  | Other, Other + SGLT2, SOC                                                    | 1407         |
| ISRCTN60069084        | Oman                     | HOSP  | Other, SOC                                                                   | 1180         |
| NCT04472728           | United States            | HOSP  | Other, SOC                                                                   | 310          |
| NCT04408040           | United States            | HOSP  | Plasma based therapy                                                         | 700          |
| NCT04393727           | Italy                    | HOSP  | Plasma based therapy                                                         | 126          |
| NCT04344535           | United States            | HOSP  | Plasma based therapy, SOC                                                   | 500          |
| NCT04429854           | Belgium                  | HOSP  | Plasma based therapy, SOC                                                   | 483          |
| NL8633                | Netherlands              | HOSP  | Plasma based therapy, SOC                                                   | 430          |
| NCT Number     | Country       | Phase | Intervention                                                                 |
|---------------|---------------|-------|-----------------------------------------------------------------------------|
| NCT04479163   | Argentina     | HOSP  | Plasma based therapy, SOC                                                   |
| ISRCTN85216856| Ecuador       | HOSP  | Plasma based therapy, SOC                                                   |
| NCT04358939   | France        | HOSP  | Positioning, SOC                                                            |
| NCT04366856   | France        | HOSP  | Positioning, SOC                                                            |
| NCT04383613   | Canada        | HOSP  | Positioning, SOC                                                            |
| ISRCTN54917435| Sweden        | HOSP  | Positioning, SOC                                                            |
| NCT04343963   | Mexico        | HOSP  | Pyridostigmine, SOC                                                         |
| 2020-001497-30| France        | HOSP  | ravilizumab (complement inhibitor), SOC                                     |
| 2020-001786-36| Belgium       | HOSP  | Recombinant interleukin 7, SOC                                              |
| 2020-001573-78| United States | HOSP  | Recombinant interleukin 7, SOC                                              |
| 2020-001453-49| France        | HOSP  | Remdesivir                                                                  |
| NCT04409262   | United States | HOSP  | Remdesivir, Remdesivir + TCZ                                                |
| 2020-001052-18| Denmark       | HOSP  | Remdesivir, SOC                                                             |
| ISRCTN13035264| Denmark       | HOSP  | Remdesivir, SOC                                                             |
| NCT04359901   | United States | HOSP  | Sarilumab, SOC                                                              |
| 2020-001473-79| Italy         | HOSP  | SGLT2, SOC                                                                  |
| NCT04389450   | United States | HOSP  | SOC, Stem cells                                                             |
| CHICTR2000029990| China      | HOSP  | SOC, Stem cells                                                             |
| NCT04366271   | Spain         | HOSP  | SOC, Stem cells                                                             |
| NCT04393415   | Egypt         | HOSP  | SOC, Stem cells                                                             |
| CTRI/2020/05/025369| India   | HOSP  | SOC, TCZ                                                                    |
| NCT04411446   | Argentina     | HOSP  | SOC, Vitamins                                                               |
| ACTRN126200000454476| Australia | HOSP  | SOC, Zinc                                                                   |
| 2020-001210-37| France        | HOSP  | sodium nitrite, SOC                                                         |
| 2020-002060-31| Czechia       | HOSP  | SOLIDARITY TRIAL                                                            |
| ISRCTN83971151| Argentina     | HOSP  | SOLIDARITY TRIAL                                                            |
| CTRI/2020/04/024773| Argentina | HOSP  | SOLIDARITY TRIAL                                                            |
| NCT04417257   | United States | HOSP  | tenretidine, SOC                                                            |
| NCT04419623   | United States | HOSP  | TL-895 (tyrosine kinase inhibitor), SOC                                     |
| NL8504        | Netherlands   | HOSP  | TCZ                                                                         |
| NCT04378920   | France        | HOSP  | trancrocetin (NMDA inhibitor), SOC                                          |
| 2020-001264-28| Bulgaria      | HOSP  | vidofludimus (pyrimidine synthesis inhibitor), SC                           |
| NCT04453384   | France        | HOSP  | XAV19 (spike protein antibody), SOC                                         |
| NCT04373707   | France        | HOSP  | Anticoagulants                                                              |
| NCT04345848   | Switzerland   | HOSP  | Anticoagulants                                                              |
| CTRI/2020/06/026193| India    | HOSP  | HCQ +/- AZM, HCQ + Lithium +/- AZM                                          |
| Study ID          | Country         | Region | Study Type | Interventions                                                                 | Participants |
|-------------------|-----------------|--------|------------|-------------------------------------------------------------------------------|--------------|
| NCT04321616       | Norway          | NA     | HOSP       | HCQ, Remdesivir, SOC                                                          | 700          |
| 2020-001754-21    | France          | NA     | HOSP       | JAKi + TCZ or Anakinra, SOC, TCZ or Anakinra                                 | 150          |
| NCT04346797       | France          | NA     | HOSP       | mAb, SOC                                                                      | 120          |
| NCT04347681       | Saudi Arabia    | NA     | HOSP       | Plasma based therapy                                                          | 575          |
| NCT04474340       | Kuwait          | NA     | HOSP       | Plasma based therapy, SOC                                                     | 300          |
| NCT04361253       | United States   | NA     | HOSP       | Plasma based therapy, SOC                                                     | 220          |
| NCT04401150       | Canada          | NA     | HOSP       | SOC, Vitamins                                                                 | 800          |
| NCT04498936       | Egypt           | NA     | HOSP       | Sofosbuvir/Ledipasvir and Nitazoxanide, DAA, SOC                              | 240          |
| NCT04363853       | United States   | NA     | HOSP       | Acalabrutinib, SOC                                                            | 177          |
| NCT04409836       | France          | NA     | HOSP       | Anticoagulants                                                               | 100�          |
| NCT04401150       | Canada          | NA     | HOSP       | Anticoagulants, Anticoagulants + Antiplatelets                               | 750          |
| NCT04365803       | United States   | NA     | HOSP       | Plasma based therapy                                                         | 200�          |
| NCT04371367       | Argentina       | NA     | HOSP       | Acpalabrutinib, SOC                                                           | 177          |
| NCT04363853       | Mexico          | NA     | HOSP       | Anticoagulants                                                               | 100�          |
| NCT04409836       | Argentina       | NA     | HOSP       | Plasma based therapy                                                         | 200�          |
| NCT04367831       | United States   | NA     | HOSP       | Acpalabrutinib, SOC                                                           | 177�          |
| NCT04410983       | United States   | NA     | HOSP       | Plasma based therapy                                                         | 200�          |
| NCT04347941       | Ireland         | NA     | HOSP       | Anticoagulants, Anticoagulants + Antiplatelets                               | 750�          |
| NCT04357803       | United States   | NA     | HOSP       | Plasma based therapy                                                         | 200�          |
| NCT04350580       | France          | NA     | HOSP       | Polyvalent Immunoglobulin, SOC                                               | 138�          |
| NCT04347941       | Italy           | NA     | HOSP       | Anticoagulants, Corticosteroids                                               | 200�          |
| NCT04367831       | United States   | NA     | HOSP       | Anticoagulants, Corticosteroids + Anticoagulants                             | 200�          |
| NCT04371367       | France          | NA     | HOSP       | Acpalabrutinib, SOC                                                           | 177�          |
| NCT04355364       | France          | NA     | HOSP       | Plasma based therapy                                                         | 100�          |
| NCT044432051      | Turkey          | NA     | HOSP       | Monitoring, SOC                                                              | 100�          |
| NCT04358003       | United States   | NA     | HOSP       | Plasma based therapy                                                         | 200�          |
| NCT04350580       | France          | NA     | HOSP       | Polyvalent Immunoglobulin, SOC                                               | 138�          |
| NCT04347941       | Ireland         | NA     | HOSP       | Anticoagulants, Corticosteroids                                               | 200�          |
| JPRN-JRCT2031200126 | United States | NA | HOSP | ravinizumab (complement inhibitor), SOC                                       | 270�          |
| NCT04371393       | United States   | NA     | HOSP       | Polyvalent Immunoglobulin, SOC                                               | 138�          |
| DRKS00021238      | Germany         | NA     | HOSP       | SOC, Stem cells                                                              | 300�          |
| NCT04264533       | China           | NA     | HOSP       | SOd xinatin, SOC                                                             | 140�          |
| NCT04364009       | France          | NA     | HOSP       | Anakinra, SOC                                                                | 240�          |
| JPRN-JRCTS031200026 | Japan       | NA | HOSP | Anticoagulants, FPV                                                        | 160�          |
| PACTR202007606032743 | Egypt     | NA | HOSP | Polyvalent Immunoglobulin, SOC                                               | 138�          |
| NCT04342051      | Turkey          | NA     | HOSP       | Monitoring, SOC                                                              | 100�          |
| DRKS00021238      | Germany         | NA     | HOSP       | Plasma based therapy                                                         | 200�          |
| NCT04365080       | France          | NA     | HOSP       | Polyvalent Immunoglobulin, SOC                                               | 138�          |
| JPRN-JRCTS031200026 | Japan       | NA | HOSP | Anticoagulants, FPV                                                        | 160�          |
| PACTR202007606032743 | Egypt     | NA | HOSP | Polyvalent Immunoglobulin, SOC                                               | 138�          |
| NCT04364009       | France          | NA     | HOSP       | Anticoagulants, SOC                                                          | 100�          |
| KCT0005105        | South Korea     | NA     | HOSP       | Corticosteroids, HCQ + Corticosteroids, SOC                                 | 141�          |
| NCT04361474       | France          | NA     | HOSP       | Corticosteroids, SOC                                                         | 120�          |
| NCT04530409       | Egypt           | NA     | HOSP       | Dexamethasone                                                                | 450�          |
| NCT04384588       | Chile           | NA     | HOSP       | Plasma based therapy                                                         | 100�          |
| CTRI/2020/06/025803 | India       | NA | HOSP | Plasma based therapy, SOC                                                      | 400�          |
| NCT04425915       | India           | NA     | HOSP       | Plasma based therapy, SOC                                                     | 400�          |
| NCT044345419      | Egypt           | NA     | HOSP       | Remdesivir, Chloroquine, SOC                                                  | 120�          |
| 2020-001390-76    | Italy           | NA     | HOSP       | Sarilumab, SOC                                                               | 171�          |
| NCT04486144       | United States   | NA     | OUTPAT     | Alternative therapy, SOC                                                     | 100�          |
| NCT number | Country | Start Date | Study Design | Interventions |
|------------|---------|------------|--------------|---------------|
| NCT04438850 | Italy | 2020-Aug | OUTPAT | HCQ |
| NCT0437918  | Canada | 2020-Aug | OUTPAT | Non-invasive respiratory support |
| NCT04369365 | Austria | 2020-Aug | OUTPAT | AZM, SOC |
| CHICTR2000029601 | China | 2020-Aug | OUTPAT | Education, Education + Herbal tea |
| NCT04466540  | Brazil | 2020-Aug | OUTPAT | Plasma based therapy, SOC |
| NCT04438057 | United States | 2020-Aug | OUTPAT | Niazoxanide, SOC |
| NCT04356495  | France | 2020-Dec | OUTPAT | Antihypertensive, FPV, HCQ, Other, SOC |
| NCT04532931 | South Africa | 2020-Dec | OUTPAT | Antimalarial, DAA, FPV + Antivirals, SOC |
| NCT04322682  | United States | 2020-Dec | OUTPAT | Azithromycin, SOC |
| NCT04322565 | Italy | 2020-Dec | OUTPAT | HCQ |
| NCT04334382  | United States | 2020-Dec | OUTPAT | HCQ vs AZM |
| CHICTR2000029741 | China | 2020-Dec | OUTPAT | HCQ, LPV/r |
| NCT04372628  | United States | 2020-Dec | OUTPAT | HCQ, LPV/r, SOC |
| NCT04529525  | Argentina | 2020-Dec | OUTPAT | Ivermectin, SOC |
| NCT0446377  | United States | 2020-Dec | OUTPAT | LAM002 (lysosome activator), SOC |
| NCT04425629  | United States | 2020-Dec | OUTPAT | mAB, SOC |
| NCT0432728   | United States | 2020-Dec | OUTPAT | SOC, Ascorbic Acid, Ascorbic Acid + Zinc, Zinc |
| CHICTR2000029780 | China | 2020-Dec | OUTPAT | SOC, Umifenovir |
| NCT04338074  | United States | 2020-Dec | OUTPAT | Tranexamic acid |
| NCT04464408 | Saudi Arabia | 2020-Dec | OUTPAT | FPV, SOC |
| CHICTR2000029721 | China | 2020-Dec | OUTPAT | Plasma based therapy, SOC |
| NCT04346667  | Pakistan | 2020-May | OUTPAT | HCQ, SOC |
| NCT04351191  | Pakistan | 2020-May | OUTPAT | HCQ, SOC |
| NCT04345991  | France | 2020-May | OUTPAT | Plasma based therapy, SOC |
| NCT04416399  | United Kingdom | 2020-Nov | OUTPAT | Corticosteroids, SOC |
| NCT04517422  | Mexico | 2020-Nov | OUTPAT | Nutrition, SOC |
| NCT04486313  | United States | 2020-Oct | OUTPAT | Antivirals + Vitamins, Vitamins |
| NCT04363827  | Italy | 2020-Sep | OUTPAT | HCQ, SOC |
| NCT04332107  | United States | 2020-Sep | OUTPAT | AZM, SOC |
| NCT04381962  | United Kingdom | 2020-Sep | OUTPAT | AZM, SOC |
| NCT04416334  | Spain | 2020-Sep | OUTPAT | Colchicine, SOC |
| NCT04377711  | United States | 2020-Sep | OUTPAT | Corticosteroids, SOC |
| NCT04370782  | United States | 2020-Sep | OUTPAT | HCQ + AZM+ Zinc, HCQ + Zinc + Antibiotics |
| Study ID       | Country       | Start Date | Outpatient | Treatments                                      |
|---------------|---------------|------------|------------|------------------------------------------------|
| NCT04331600   | Poland        | 2020-Sep   | OUTPAT     | HCQ, SOC                                       |
| NCT04518410   | United States | 2020-Sep   | OUTPAT     | Other, SOC                                     |
| CHICTR2000033057 | China       | 2020-Sep   | OUTPAT     | Rehabilitation                                  |
| NCT04427501   | United States | 2020-Sep   | OUTPAT     | mAB, SOC                                       |
| NCT04329923   | United States | 2021-Apr   | OUTPAT     | HCQ, SOC                                       |
| NCT04390503   | United States | 2021-Apr   | OUTPAT     | Plasma based therapy, SOC                      |
| NCT04311177   | United States | 2021-Apr   | OUTPAT     | ARBs, SOC                                      |
| NCT04523090   | South Africa  | 2021-Apr   | OUTPAT     | Nitozoxanide                                   |
| CHICTR2000029589 | China      | 2021-Dec   | OUTPAT     | SOC, Herbal tea                                |
| CHICTR2000029539 | China      | 2021-Feb   | OUTPAT     | LPV/r, SOC                                     |
| NCT04460690   | United States | 2021-Jul   | OUTPAT     | Rapid SARS-Cov-2 detection                     |
| NCT04475601   | Sweden        | 2021-Jul   | OUTPAT     | Hormone therapy, SOC                           |
| NCT04342689   | United States | 2021-Jun   | OUTPAT     | Nutrition, SOC                                 |
| NCT04418505   | United States | 2021-Mar   | OUTPAT     | Alternative therapy, SOC                       |
| NCT04357990   | Iceland       | 2021-Mar   | OUTPAT     | Alternative therapy, SOC                       |
| NCT04400799   | Switzerland   | 2021-Mar   | OUTPAT     | Anticoagulants, SOC                            |
| CHICTR2000030804 | China       | 2021-Mar   | OUTPAT     | SOC, Herbal tea                                |
| NCT04353284   | United States | 2021-May   | OUTPAT     | Camostat, SOC                                  |
| NCT04331899   | United States | 2021-May   | OUTPAT     | IFN, SOC                                       |
| NCT04342169   | United States | 2022-Apr   | OUTPAT     | HCQ, SOC                                       |
| NCT04373460   | United States | 2022-Dec   | OUTPAT     | Plasma based therapy, SOC                      |
| NCT04355767   | United States | 2022-Dec   | OUTPAT     | Plasma based therapy, SOC                      |
| CHICTR2000030084 | China       | 2022-Feb   | OUTPAT     | Psychological therapy, SOC                     |
| CTRI/2020/05/025490 | India      | NA        | OUTPAT     | Alternative therapy, SOC                       |
| NCT04404218   | Canada        | NA         | OUTPAT     | Acai Berry, SOC                                |
| ISRCTN13311119 | India        | NA         | OUTPAT     | Alternative therapy, SOC                       |
| JPRN-UMIN0000040602 | Brazil    | NA         | OUTPAT     | Alternative therapy, SOC                       |
| ISRCTN59048638 | Mexico       | NA         | OUTPAT     | Anticoagulants, SOC                            |
| NCT04365582   | France        | NA         | OUTPAT     | AZM, HCQ, LPV/r, SOC                           |
| NCT04359329   | United States | NA         | OUTPAT     | Estrogen steroid hormone, SOC                  |
| 2020-002106-68 | United Kingdom | NA     | OUTPAT     | FPV, LPV/r, LPV/r + FPV, SOC                   |
| NCT04346628   | United States | NA         | OUTPAT     | FPV, SOC                                       |
| ISRCTN86534580 | United Kingdom | NA     | OUTPAT     | HCQ, SOC                                       |
| 2020-001469-35 | Poland        | NA         | OUTPAT     | HCQ, SOC                                       |
| NCT04351516   | Germany       | NA         | OUTPAT     | HCQ, SOC                                       |
| 2020-001558-23 | Italy         | NA         | OUTPAT     | HCQ, SOC                                       |
| NCT Number       | Country    | Region | Study Design | Treatment/Inclusion                                                                 | Trials | Pts  |
|------------------|------------|--------|--------------|------------------------------------------------------------------------------------|--------|------|
| NCT04446429      | Brazil     | NA     | OUTPAT       | Hormone therapy + Ivermectin + AZM, Ivermectin + AZM                              |        | 381  |
| NCT04382131      | United Kingdom | NA     | OUTPAT       | Hygiene, SOC                                                                        |        | 405  |
| NCT044141124     | United States | NA     | OUTPAT       | Ivermectin, SOC                                                                   |        | 100  |
| NCT044141124     | United States | NA     | OUTPAT       | KB109 (glycan), SOC                                                               |        | 400  |
| NCT04455570      | United States | NA     | OUTPAT       | molnupiravir N4-hydroxycytidine derivative, SOC                                   |        | 108  |
| CHICTR2000029387 | China      | NA     | OUTPAT       | Ribavirin + IFN, Ribavirin + LPV/r + IFN, LPV/r + IFN                             |        | 108  |
| CHICTR2000029855 | China      | NA     | OUTPAT       | SOC, Herbal tea                                                                   |        | 180  |
| CHICTR2000029855 | China      | NA     | OUTPAT       | SOC, Vitamin D                                                                    |        | 140  |
| CHICTR2000030481 | China      | 2020-Apr | OUTPAT, HOSP | Thymoquinone, SOC                                                                |        | 100  |
| CHICTR2000030471 | China      | 2020-Apr | OUTPAT, HOSP | Corticosteroids, SOC                                                              |        | 200  |
| CHICTR2000029518 | China      | 2020-Apr | OUTPAT, HOSP | Nutrition, SOC                                                                    |        | 394  |
| CHICTR2000029974 | China      | 2020-Aug | OUTPAT, HOSP | SOC, Herbal tea                                                                   |        | 140  |
| NCT04467918      | Brazil     | 2020-Aug | OUTPAT, HOSP | SOC, Herbal tea                                                                   |        | 300  |
| NCT04455570      | United States | 2020-Aug | OUTPAT, HOSP | Alternative therapy, SOC                                                          |        | 100  |
| CHICTR2000033318 | China      | 2020-Dec | OUTPAT, HOSP | Exercise, SOC                                                                     |        | 104  |
| NCT04529499      | Kuwait     | 2020-Dec | OUTPAT, HOSP | FPV, SOC                                                                           |        | 780  |
| NCT04324463      | Brazil     | 2020-Dec | OUTPAT, HOSP | HCQ + AZM, SOC                                                                    |        | 4000 |
| NCT04393038      | Belgium    | 2020-Dec | OUTPAT, HOSP | Other, SOC                                                                        |        | 1034 |
| CHICTR2000029954 | China      | 2020-Feb | OUTPAT, HOSP | SOC, Herbal tea                                                                   |        | 300  |
| CHICTR2000030102 | China      | 2020-May | OUTPAT, HOSP | Non-invasive respiratory support, SOC                                              |        | 180  |
| NCT04338828      | United States | 2021-Apr | OUTPAT, HOSP | Nitric Oxide, SOC                                                                |        | 260  |
| NCT04390191      | United States | 2021-Apr | OUTPAT, HOSP | Non-invasive respiratory support, SOC                                              |        | 200  |
| NCT04517396      | United States | 2021-Aug | OUTPAT, HOSP | BIO101 (MAS activator), SOC                                                      |        | 300  |
| IRCT20190810044500N5 | Iran    | 2021-Feb | OUTPAT, HOSP | Colchicine, HCQ + Colchicine                                                      |        | 200  |
| Study Identifier   | Country      | Start Date | Study Type | Intervention                                                                 | Controls |赋值 |
|-------------------|--------------|------------|------------|-------------------------------------------------------------------------------|----------|-----|
| CHICTR2000029867  | China        | 2021-Feb   | OUTPAT, HOSP | Carrimycin, LPV/r                                                             |          | 520 |
| NCT04394117       | Australia    | 2021-Jan   | OUTPAT, HOSP | ARBs, SOC                                                                   |          | 605 |
| NCT04419025       | United States| 2021-Jan   | OUTPAT, HOSP | N-acetyl ccysteine                                                            |          | 200 |
| NCT04500418       | Germany      | 2021-Sep   | OUTPAT, HOSP | cenicriviroc (CCR2 and CCR5 receptor blocker), SOC                            |          | 183 |
| CTRI/2020/06/025763 | India     | NA         | OUTPAT, HOSP | Alternative therapy                                                           |          | 150 |
| ISRCTN14212905    | United Kingdom| NA         | OUTPAT, HOSP | Anticoagulants, Other, SOC                                                   |          | 100 |
| 2020-001498-63     | Belgium      | NA         | OUTPAT, HOSP | BIO101 (MAS activator)                                                       |          | 465 |
| CHICTR2000029573  | China        | NA         | OUTPAT, HOSP | cytokine derived gene protein, SOC                                            |          | 480 |
| NCT04445467       | Australia    | NA         | OUTPAT, HOSP | FPV, SOC                                                                     |          | 190 |
| NCT04336332       | United States| NA         | OUTPAT, HOSP | HCQ, HCQ + AZM, SOC                                                          |          | 160 |
| NCT04385095       | United Kingdom| NA         | OUTPAT, HOSP | IFN, SOC                                                                     |          | 820 |
| ISRCTN14241621    | United Kingdom| NA         | OUTPAT, HOSP | IFN, SOC                                                                     |          | 220 |
| NCT04354259       | Canada       | NA         | OUTPAT, HOSP | IFN, SOC                                                                     |          | 140 |
| 2020-001860-27     | United Kingdom| NA         | OUTPAT, HOSP | multiple drugs, SOC                                                          |          | 250 |
| NCT04377308       | United States| NA         | OUTPAT, HOSP | SOC, SSRIs                                                                   |          | 2000 |
| 2020-001501-24     | Italy        | NA         | PREV         | HCQ, SOC                                                                     |          | 2300 |
| NCT04374942       | Canada       | 2020-Aug   | PREV         | HCQ, SOC                                                                     |          | 988 |
| NCT04359537       | Pakistan     | 2020-Aug   | PREV         | HCQ, SOC                                                                     |          | 200 |
| CHICTR2000029602  | China        | 2020-Aug   | PREV         | Education + Monitoring + Herbal tea, Psychological therapy                  |          | 600 |
| NCT04380701       | Germany      | 2020-Aug   | PREV         | BNT162 RNA Vaccine                                                           |          | 200 |
| NCT04334928       | Spain        | 2020-Dec   | PREV         | HCQ, HCQ + NRTIs, NRTIs, SOC                                                |          | 4000 |
| NCT04318015       | Mexico       | 2020-Dec   | PREV         | HCQ, SOC                                                                     |          | 400 |
| NCT04348435       | United States| 2020-Dec   | PREV         | SOc, Stem cells                                                              |          | 100 |
| CHICTR2000031944  | China        | 2020-Dec   | PREV         | SOc, Herbal Tea                                                              |          | 2000 |
| NCT04530357       | Kazakhstan   | 2020-Dec   | PREV         | QAZ-Covid Inactivated Vaccine, SOC                                            |          | 244 |

注：本预印版（which was not certified by peer review）由授权者/资助者授予medRxiv许可，允许预印版的永久发表。
| NCT Number | Location       | Start Date | Type   | Interventions                                                                 |
|------------|----------------|------------|--------|-------------------------------------------------------------------------------|
| NCT04344379 | France         | 2020-Jul   | PREV   | AZM, HCQ, SOC                                                                |
| NCT04349228 | Tunisia        | 2020-Jul   | PREV   | HCQ, SOC                                                                     |
| NCT04366180 | Spain          | 2020-Jun   | PREV   | Nutrition, SOC                                                               |
| NCT04320238 | China          | 2020-May   | PREV   | IFN, IFN + Other                                                             |
| NCT04421391 | United States  | 2020-Nov   | PREV   | Nutrition                                                                     |
| NCT04466280 | Iran           | 2020-Nov   | PREV   | HCQ + mucodentol, mucodentol                                                  |
| NCT04352933 | United Kingdom | 2020-Oct   | PREV   | HCQ, SOC                                                                     |
| NCT04521322 | Argentina      | 2020-Oct   | PREV   | Iota-Carageenan                                                              |
| NCT04353128 | Spain          | 2020-Oct   | PREV   | Melatonin, SOC                                                               |
| NCT04313023 | United States  | 2020-Oct   | PREV   | PUL-042 (toll-like receptor agonists, SOC)                                    |
|             | Iran           | 2020-Oct   | PREV   | SOC, Vitamin D3                                                              |
| NCT04405908 | Australia      | 2020-Oct   | PREV   | SCB019 (Clover), SOC                                                         |
| NCT04495933 | Australia      | 2020-Oct   | PREV   | SOC, M59 sclamp Vaccine                                                      |
| NCT04384458 | Brazil         | 2020-Sep   | PREV   | HCQ, SOC                                                                     |
| NCT04409327 | United States  | 2020-Sep   | PREV   | Other, SOC                                                                   |
| NCT04303507 | Thailand       | 2021-Apr   | PREV   | HCQ, SOC                                                                     |
| NCT04349371 | United States  | 2021-Apr   | PREV   | HCQ, SOC                                                                     |
| NCT04312243 | United States  | 2021-Apr   | PREV   | Non-invasive respiratory support, SOC                                         |
| NCT04353037 | United States  | 2021-Apr   | PREV   | HCQ, SOC                                                                     |
| NCT04435808 | United States  | 2021-Apr   | PREV   | HCQ, SOC                                                                     |
| NCT04321928 | Hungary        | 2021-Apr   | PREV   | Education, Psychological therapy                                             |
| NCT04368728 | United States  | 2021-Apr   | PREV   | SOC, Vaccine Pfizer Biontech mRNA Vaccine                                     |
| NCT04333732 | United States  | 2021-Aug   | PREV   | HCQ, SOC                                                                     |
| NCT04494276 | Belgium        | 2021-Aug   | PREV   | SOC, CVnCov Vaccine                                                           |
| NCT04461379 | Mexico         | 2021-Jan   | PREV   | SOC, Vaccine                                                                 |
| CHICTR2000034780 | China     | 2021-Jul   | PREV   | SOC, Vaccine                                                                 |
| IRCT20200011047019N1 | Iran | 2021-Jun   | PREV   | SOC, BCG                                                                     |
| NCT04327206 | Australia      | 2021-Jun   | PREV   | Vaccine                                                                      |
| NCT04471519 | India          | 2021-Jun   | PREV   | SOC, Vaccine                                                                 |
| NCT04363450 | United States  | 2021-Mar   | PREV   | HCQ, SOC                                                                     |
| NCT04448119 | Canada         | 2021-Mar   | PREV   | FPV, SOC                                                                     |
| NCT04364022 | Switzerland    | 2021-Mar   | PREV   | HCQ, LPV/r                                                                   |
| NCT04318444 | United States  | 2021-Mar   | PREV   | HCQ, SOC                                                                     |
| NCT04321174 | Canada         | 2021-Mar   | PREV   | LPV/r, SOC                                                                   |
| NCT04348370 | United States  | 2021-May   | PREV   | SOC, Vaccine                                                                 |
| NCT04364802 | United States  | 2021-May   | PREV   | Hygiene, SOC                                                                 |
| NCT Number   | Country     | Start Date | Intervention  | Description                                                                 |
|-------------|-------------|------------|---------------|-----------------------------------------------------------------------------|
| NCT04414267 | Greece      | 2021-May   | PREV          | SOC, Vaccine                                                                |
| NCT04530396 | Russia      | 2021-May   | PREV          | SOC, Vaccine Russian Gamelaya Vaccine                                         |
| NCT04519437 | United States| 2021-Oct   | PREV          | mAb, SOC                                                                    |
| NCT04456595 | Brazil      | 2021-Sep   | PREV          | SOC, Vaccine                                                                |
| NCT04536051 | Brazil      | 2021-Sep   | PREV          | Vaccine                                                                     |
| NCT04537949 | Germany     | 2021-Sep   | PREV          | BNT162 RNA Vaccine                                                          |
| NCT04466085 | China       | 2021-Sep   | PREV          | SOC, Vaccine                                                                |
| NCT04372017 | United States| 2022-Apr   | PREV          | HCQ, Vitamins                                                               |
| NCT04323800 | United States| 2022-Dec   | PREV          | Plasma based therapy, SOC                                                   |
| NCT04447781 | South Korea | 2022-Feb   | PREV          | Device, INO4800 + Device                                                   |
| NCT04299724 | China       | 2023-Jul   | PREV          | aAPC Vaccine                                                                |
| ACTRN12620000417987 | Australia | NA               | PREV          | HCQ                                                                         |
| NCT04340349 | Mexico      | NA         | PREV          | HCQ, bromhexine, SOC                                                        |
| CTRI/2020/05/025067 | India | NA       | PREV          | HCQ, SOC                                                                    |
| ACTRN12620000501943 | Australia | NA               | PREV          | HCQ, SOC                                                                    |
| NCT04334148 | United States| NA         | PREV          | HCQ, SOC                                                                    |
| 2020-001987-28 | Italy     | NA         | PREV          | HCQ, SOC                                                                    |
| NCT04349228 | Tunisia     | NA         | PREV          | HCQ, SOC                                                                    |
| NCT04496245 | Australia   | NA         | PREV          | Immunomodulators, SOC                                                       |
| NCT04452773 | Spain       | NA         | PREV          | Manremyc food supplement                                                    |
| NCT04408183 | United States| NA         | PREV          | quinine topical nasal spary                                                  |
| NCT04379336 | South Africa| NA         | PREV          | SOC, BCG                                                                    |
| ISRCTN50212645 | United Kingdom | NA   | PREV          | Other                                                                       |
| CTRI/2020/05/025429 | India | NA       | PREV          | Alternative therapy, SOC                                                    |
| NCT04343248 | United States| NA         | PREV          | Antivirals, SOC                                                             |
| SLCTR/2020/011 | Sri Lanka | NA       | PREV          | HCQ, SOC                                                                    |
| CTRI/2020/06/025928 | India | NA       | PREV          | Hygiene                                                                     |
| NCT04344600 | United States| NA         | PREV          | IFN, SOC                                                                    |
| NCT04399252 | United States| NA         | PREV          | Nutrition, SOC                                                              |
| CTRI/2020/05/025277 | India | NA       | PREV          | Other, SOC                                                                  |
| CHICTR20000032459 | China | NA       | PREV          | SOC, Inactivated SARS-Cov-2 (Vero cell) Vaccine                             |
| NCT04475302 | India       | NA         | PREV          | SOC, Vaccine                                                                |
| NCT04368988 | United States| NA         | PREV          | SOC, Vaccine                                                                |
| NCT | Country          | Region | Sex/Age Groups | Intervention                                                      |
|-----|------------------|--------|----------------|------------------------------------------------------------------|
| NCT04369794 | Brazil          | NA     | PREV           | SOC, Vaccine                                                       |
| NCT04470427 | United States   | NA     | PREV           | SOC, Vaccine mRNA1273                                              |
| CTRI/2020/06/025769 | India     | NA     | PREV           | Alternative therapy, SOC                                          |
| CTRI/2020/05/025484 | India     | NA     | PREV           | Alternative therapy, SOC                                          |
| CTRI/2020/05/025491 | India     | NA     | PREV           | Alternative therapy, SOC                                          |
| CTRI/2020/07/026560 | India     | NA     | PREV           | Alternative therapy, SOC                                          |
| IRCT20130306012728N8 | Iran      | NA     | PREV           | HCQ, SOC                                                         |
| NCT04387409 | Germany         | NA     | PREV           | SOC, Vaccine                                                      |
| NCT04384549 | France          | NA     | PREV           | SOC, Vaccine                                                      |
| CTRI/2020/06/025861 | India     | NA     | PREV           | Alternative therapy, SOC                                          |

**Notes:**
- CC-BY-NC-ND 4.0 International license
- The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
| NCT number      | Country       | Date       | Overall Status | Tail | Description                          | Participants |
|-----------------|---------------|------------|----------------|------|--------------------------------------|--------------|
| NCT04365309     | China         | 2020-Apr   | UNCLEAR        | Tail | Antihypertensive, SOC                | 128          |
| NCT04319900     | China         | 2020-Apr   | UNCLEAR        | Tail | FPV, HCQ + FPV, SOC                  | 150          |
| NCT04326790     | Gibraltar     | 2020-Aug   | UNCLEAR        | Tail | Colchicine, SOC                      | 180          |
| NCT04527562     | Bangladesh    | 2020-Dec   | UNCLEAR        | Tail | Ivermectin + ARBs, SOC               | 176          |
| NCT04323345     | Egypt         | 2020-Dec   | UNCLEAR        | Tail | Nutrition, SOC                       | 1000         |
| NCT04447235     | Brazil        | 2020-Dec   | UNCLEAR        | Tail | HCQ, AZM, SOC                        | 240          |
| NCT04425707     | Egypt         | 2020-Jul   | UNCLEAR        | Tail | Ivermectin, SOC                      | 100          |
| NCT04447235     | China         | 2020-Dec   | UNCLEAR        | Tail | SOC, Herbal tea                      | 200          |
| NCT04334265     | China         | 2020-Jun   | UNCLEAR        | Tail | Alternative therapy, SOC             | 750          |
| NCT04392141     | Iran          | 2020-Jun   | UNCLEAR        | Tail | Colchicine + Alternative therapy, SOC | 200          |
| NCT04323345     | China         | 2020-Dec   | UNCLEAR        | Tail | SOC, Herbal tea                      | 200          |
| NCT04447235     | China         | 2020-Dec   | UNCLEAR        | Tail | SOC, Herbal tea                      | 200          |
| NCT04447235     | China         | 2020-Dec   | UNCLEAR        | Tail | SOC, Herbal tea                      | 200          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 120          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | LPV/r + IFN, LPV/r + IFN + Other     | 100          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | SOC, Herbal tea                      | 300          |
| NCT04392141     | China         | 2020-Jun   | UNCLEAR        | Tail | Herbal tea                           | 100          |
| Identifier       | Country       | Start Date | Duration | Notes                                                                 |
|------------------|---------------|------------|----------|----------------------------------------------------------------------|
| CHICTR2000029790 | China         | 2020-Oct   | UNCLEAR  | SOC, Herbal tea                                                        |
| NCT04353336      | Egypt         | 2020-Sep   | UNCLEAR  | HCQ                                                                  |
| NCT04325893      | France        | 2020-Sep   | UNCLEAR  | HCO, SOC                                                              |
| NCT04429711      | Israel        | 2020-Sep   | UNCLEAR  | Ivermectin, SOC                                                       |
| NCT04463264      | Argentina     | 2020-Sep   | UNCLEAR  | Nitazoxanide, SOC                                                    |
| NCT04338698      | Pakistan      | 2020-Sep   | UNCLEAR  | Oseltamavir vs Azithromycin vs HCQ                                    |
| NCT04449588      | China         | 2021-Aug   | UNCLEAR  | BDB001 (toll like receptor agonist), SOC                              |
| CHICTR2000030117 | China         | 2021-Dec   | UNCLEAR  | LPV/r + IFN, Herbal tea                                              |
| CHICTR2000029935 | China         | 2021-Feb   | UNCLEAR  | HCQ                                                                  |
| CHICTR2000029939 | China         | 2021-Feb   | UNCLEAR  | HCQ, SOC                                                              |
| NCT04421508      | United States | 2021-Feb   | UNCLEAR  | Non-invasive respiratory support, SOC                                |
| CHICTR2000029605 | China         | 2021-Feb   | UNCLEAR  | SOC, Herbal tea                                                       |
| CHICTR2000029747 | China         | 2021-Feb   | UNCLEAR  | SOC, Herbal tea                                                       |
| IRCT20110726007117N11 | Iran | 2021-Jan | UNCLEAR  | SOC, Vitamin D                                                        |
| NCT04334512      | United States | 2021-Jun   | UNCLEAR  | HCQ, AZM, Vitamins, Zinc                                             |
| NCT04344041      | France        | 2021-May   | UNCLEAR  | ,Vitamin D, SOC                                                       |
| CHICTR2000032919 | China         | 2021-May   | UNCLEAR  | SOC, Herbal tea                                                       |
| NCT04395768      | Australia     | 2021-Sep   | UNCLEAR  | HCQ + AZM + Zinc + Vitamins                                          |
| CHICTR2000029756 | China         | 2022-Feb   | UNCLEAR  | IFN, Herbal tea                                                       |
| CHICTR2000029976 | China         | 2022-Feb   | UNCLEAR  | Psychological therapy, SOC                                           |
| CTRI/2020/06/026221 | India      | NA         | UNCLEAR  | Alternative therapy, HCQ                                             |
| CTRI/2020/06/025557 | India     | NA         | UNCLEAR  | Alternative therapy, SOC                                             |
| CTRI/2020/07/026468 | India      | NA         | UNCLEAR  | Alternative therapy, SOC                                             |
| NCT04351347      | Egypt         | NA         | UNCLEAR  | Antivirals, HCQ, Ivermectin                                          |
| CHICTR2000032769 | China         | NA         | UNCLEAR  | Azuvidine, SOC                                                       |
| NCT04471766      | Guinea-Bissau | NA         | UNCLEAR  | Cloth face mask, SOC                                                 |
| CTRI/2020/05/025320 | India      | NA         | UNCLEAR  | Exercise + Nutrition + Hygiene + Alternative therapy + Other, SOC    |
| CTRI/2020/06/025575 | India     | NA         | UNCLEAR  | HCQ + ribavirin, LPV/r + ribavirin                                   |
| NCT04374019      | United States | NA         | UNCLEAR  | HCQ, HCQ + AZM, HCQ + Ivermectin, Other                             |
| NCT04447534      | Egypt         | NA         | UNCLEAR  | HCQ, HCQ + Zinc                                                      |
| NCT04403555      | Egypt         | NA         | UNCLEAR  | HCQ, Ivermectin + Doxycine                                          |
| NCT04410562      | Spain         | NA         | UNCLEAR  | HCQ, SOC                                                             |
| NCT04352959      | France        | NA         | UNCLEAR  | Hygiene, SOC                                                          |
| RPCEC0000000307   | Cuba          | NA         | UNCLEAR  | IFN                                                                  |
| CHICTR2000029638 | China         | NA         | UNCLEAR  | IFN                                                                  |
| CHICTR2000030262 | China         | NA         | UNCLEAR  | IFN, SOC                                                             |
| ID            | Country        | Completion | Patient setting        | Treatment                                                                 |
|---------------|----------------|------------|------------------------|---------------------------------------------------------------------------|
| NCT04255017   | China          | NA         | UNCLEAR                | LPV/r, Oseltamivir, SOC, Umifenovir                                         |
| NCT04495816   | United States  | NA         | UNCLEAR                | Nutrition, SOC                                                            |
| NCT04407390   | Denmark        | NA         | UNCLEAR                | SOC, nicotamid riboside                                                  |
| NCT04510207   | Bahrain        | NA         | UNCLEAR                | SOC, Vaccine Wuhan Institute of Biological Products Vero cell            |
| JPRN-JRCTS061200002 | Japan    | NA         | UNCLEAR                | teprenone, SOC                                                           |
| NCT044254874  | China          | NA         | UNCLEAR                | Umifenovir, Umifenovir + IFN                                              |
| NCT04407286   | United States  | NA         | UNCLEAR                | Vitamin D                                                                |
| NCT04432607   | United States  | 2021-Jan   | Outpatient             | DHODH inhibitor brequinar. SOC                                            |
| NCT044570538  | United States  | 2021-Mar   | Healthy Unexposed       | SOC, GAM-Covid Vaccine                                                    |
| NCT04610567   | Brazil         | 2021-Mar   | Hospital               | Methotrexae, SOC                                                         |
| NCT04509999   | United States  | 2022-Sep   | Outpatient             | Other, SOC                                                               |
| NCT04432324   | Spain          | 2020-Dec   | Hospital               | iViG                                                                     |
| NCT04377568   | Canada         | 2021-Dec   | Hospital               | Plasma based therapy, SOC                                                |
| NCT04392713   | Pakistan       | NA         | NA                     | Ivermectin, SOC                                                          |
| NCT04466683   | United States  | NA         | Hospital               | Radiation therapy, SOC                                                   |
| NCT04492228   | Italy          | NA         | Hospital               | Nutrition, SOC                                                           |
| CTRI/2020/08/026957 | India    | NA         | Hospital               | Alternative therapy, SOC                                                 |
| PACTR20200676681890 | Brazil | NA         | Hospital               | Plasma based therapy, SOC                                                |
| RPCEC00000309  | Mexico         | NA         | Outpatient, Hospital, ICU| activated sodium chloride inhalation                                      |
| NCT044420676  | Austria        | NA         | Outpatient             | Nutrition, SOC                                                           |
| NCT04549922   | Brazil         | 2021-Feb   | Unclear                | Antisense therapy, SOC                                                   |
| NCT04587219   | Russia         | 2020-Dec   | NA                     | GAM-Covid vaccine                                                        |
| NCT04510493   | Switzerland    | 2023-Sep   | Hospital               | mAb, SOC                                                                |
| JPRN-JRCT2071200023 | Japan  | NA         | Unclear                | Viracept, SOC                                                            |
| CTRI/2020/06/026001 | India | NA         | Hospital               | Ivermectin, SOC                                                          |
| CTRI/2020/08/027106 | India | NA         | Hospital               | Alternative therapy, SOC                                                 |
| NCT04596085   | India          | 2020-Nov   | Outpatient             | Nutrition, SOC                                                           |
| NCT04472494   | United States  | 2021-Jan   | Hospital               | abatacept                                                               |
| NCT04410328   | United States  | 2021-Mar   | Hospital               | Anticoagulant, aggrenox                                                   |
| NCT04516759   | United Kingdom | 2021-Mar   | Hospital               | Glucokinase activator                                                    |
| NCT04551911   | United States  | 2021-Feb   | Unclear                | SOC, Vitamins rayaldee                                                   |
| NCT04604327   | Spain          | 2021-May   | Hospital               | Anticoagulants                                                           |
| NCT04576728   | Spain          | 2021-Mar   | Hospital               | SOC, Trimodulin                                                          |
| NCT04523181   | United States  | 2020-Dec   | Hospital               | Antiroquinolol                                                           |
| NCT04511650   | United States  | 2021-Feb   | Hospital               | Razuprotafib, SOC                                                       |
| NCT04428021   | Italy          | NA         | Hospital               | Plasma based therapy, SOC                                                |
| PER-013-20    | Peru           | NA         | Hospital, ICU           | Plasma based therapy, SOC                                                |
| NCT04578158   | Pakistan       | 2021-Apr   | Hospital               | Alternative therapy, SOC                                                 |
| NCT Number | Location | Period | Setting | Treatments |
|------------|----------|--------|---------|------------|
| NCT04583956 | United States | 2021-Jan | Hospital | Remdesivir, Remdesivir + mAb |
| NCT04558021 | Turkey | 2021-Jan | NA | Niclosamide |
| 2020-001329-30 | China | NA | ICU | Non-invasive respiratory support |
| ACTRN12620000557932 | Australia | NA | Hospital | HCQ + Zinc + Vitamins + AZT |
| CTRI/2020/06/025768 | India | NA | Clear | Alternative therapy |
| NCT04622865 | France | 2021-Jun | Hospital | Alternative therapy + Other, HCQ |
| NCT0437457 | France | NA | Hospital | Respiratory stimulant, SOC |
| NCT04496677 | United Kingdom | NA | Outpatient | FPV, LPV/r, LPV/r + FPV, SOC |
| NCT04523246 | United States | 2021-Jul | Nursing home residents | SOC, shingrix Vaccine |
| NCT04568031 | Japan | 2021-Sep | NA | Vaccine ChAdOx1 Vector Vaccine (non-replicating) |
| NCT04498247 | United States | 2022-Apr | NA | V591 Merck Vaccine |
| NCT04583599 | United States | 2020-Dec | Outpatient | Camostat, SOC |
| 2020-002713-17 | Mexico | NA | Hospital | Immunomodulators, mAb, SOC |
| NCT04370236 | United States | 2021-Feb | Hospital | INBO3, checkpoint inhibitor |
| NCT04455815 | United Kingdom | 2021-Aug | Outpatient | Camostat, SOC |
| NCT04530435 | Denmark | 2021-Apr | Outpatient | Respiratory support, SOC |
| NCT04535674 | Spain | NA | Hospital | Other, SOC |
| 2020-001662-11 | France | NA | Hospital | JAKi, SOC |
| NCT04603924 | United States | 2021-Jun | Hospital | Other, SOC Niclosamide |
| NCT04494646 | United States | 2021-Jan | Hospital | SOC, Triterpenes |
| NCT04435795 | Canada | 2021-Feb | Outpatient | Corticosteroids, SOC |
| NCT04581954 | United Kingdom | 2021-Jun | Hospital | Immunomodulators, JAKi, SOC |
| NCT04377750 | Israel | 2020-Apr | ICU | SOC, TCZ |
| NCT04321096 | Denmark | 2020-Dec | Hospital | Other, SOC |
| NCT04504103 | United States | 2020-Dec | Outpatient | Anticoagulants, SOC |
| CHICTR2000039000 | China | 2020-Dec | NA | SOC, Inactivated SARS Cov 2 vaccine |
| NCT04335084 | United States | 2021-Jun | Healthcare Workers | HCQ + Vitamins + Zinc, SOC |
| NCT04471636 | Germany | NA | Outpatient | Device + Other, SOC |
| NCT04589949 | Netherlands | 2022-Nov | Outpatient | Plasma-based therapy |
| NCT04376684 | United States | 2020-Dec | Hospital | mAb, SOC |
| CTRI/2020/07/026791 | India | NA | Hospital | Antihypertensive, SOC, Statins |
| NCT04350593 | United States | 2020-Oct | Hospital | SGLT2, SOC |
| NCT04504734 | United States | 2021-Feb | Outpatient | Anti-inflammatory, SOC bucillamine |
| ACTRN12620000473965 | Australia | NA | Healthcare Workers | Immunomodulators, SOC |
| NCT04492475 | United Kingdom | 2023-Nov | Hospital | Remdesivir, Remdesivir + IFN |
| 2020-001072-15 | United Kingdom | NA | Healthy Unexposed | Vaccine |
| NCT04359095 | Colombia | 2020-Nov | Hospital | AZT, HCQ, LPV/r, SOC |
| NCT04501952 | United States | 2020-Dec | Outpatient | Remdesivir, SOC |
| NCT04575584 | United States | 2021-Apr | NA | Antivirals molnupiravir, SOC |
| NCT04545060 | United States | 2021-Jan | Outpatient | Monoclonal antibody, SOC |
| NCT04606563 | United States | 2021-Jun | NA | ARBs, SOC |
| NCT04575597 | United States | 2021-Apr | Outpatient | Antivirals, SOC |
| CTRI/2020/08/027170 | India | NA | Healthy Unexposed | SOC, Vaccine Covishield |
| NCT04444674 | South Africa | 2020-Oct | NA | SOC, Vaccine ChAdOx1 nCoV-19) |
| NCT/ACTRN Number | Country       | Start Date | Setting     | Interventions                                                                 |
|------------------|---------------|------------|-------------|-------------------------------------------------------------------------------|
| NCT04593940      | United States | 2021-Feb   | Hospital    | Remdesivir + Costimulation blocker, Remdesivir + mAb, Remdesivir + Other      |
| NCT04497987      | United States | NA         | Nursing home residents | LY COV 555 monoclonal ab                                                      |
| ACTRN12620000445976 | New Zealand   | NA         | Hospital    | HCQ, LPV/r, LPV/r + HCQ                                                      |
| NCT04366960      | Italy         | 2020-Aug   | Hospital    | Anticoagulants                                                               |
| CHICTR2000030936 | China         | 2020-May   | Outpatient, Hospital | SOC, TCM                                                                      |
| NCT04508023      | United States | 2021-Mar   | NA          | Anticoagulants, SOC                                                           |
| NCT04533399      | South Africa  | NA         | Healthy Unexposed | SOC, Vaccine, Novavax vaccine                                                  |
| NCT04498273      | United States | 2021-Sep   | Outpatient  | Anticoagulants, Antihypertensive, SOC                                         |
| NCT04583995      | United Kingdom| NA         | NA          | SOC, SOC + Vaccine,,SARS-CoV-2 rS with Matrix-M1 adjuvant, Novavax vaccine    |
| 2020-001228-32    | United Kingdom| NA         | Healthy Unexposed | SOC, chadOxV vaccine astra zeneca                                              |
| NCT04582344      | Turkey        | 2021-Feb   | NA          | SOC, Vaccine.coronavac vaccine                                                 |
| 2020-001441-39    | United Kingdom| NA         | Healthcare Workers | HCQ, SOC                                                                      |
| ISRCTN10207947    | Indonesia     | NA         | Healthcare Workers | HCQ, SOC                                                                      |
| NCT04516746      | United States | 2020-Dec   | Unclear     | SOC, Vaccine, chadOxV vaccine astra zeneca                                    |
| NCT04505722      | United States | NA         | Unclear     | SOC, Vaccine, JANSEN AD26.Cov2.s                                             |
| REGISTRATION ID       | Country   | EXPECTED COMPLETION | SUBJECTS | AGENTS STUDIED                                      | NO OF SUBJECTS |
|-----------------------|-----------|----------------------|----------|-----------------------------------------------------|----------------|
| IRCT20200506047319N1  | Iran      | 2020-Jul             | HOSP     | Alternative therapy, SOC                            | 100            |
| IRCT20200607047675N1  | Iran      | 2020-Sep             | HOSP     | Alternative therapy, SOC                            | 100            |
| IRCT20200610047722N1  | Iran      | 2020-Jul             | HOSP     | Alternative therapy, SOC                            | 100            |
| IRCT20080901001165N48 | Iran      | 2020-Jun             | HOSP     | Antiretrovirals, LPV/r                              | 100            |
| IRCT20200504047298N1  | Iran      | 2020-Jun             | HOSP     | Alternative therapy, SOC                            | 100            |
| CHICTR2000032456      | China     | 2020-May             | HOSP     | Education + Non-invasive respiratory support, SOC   | 100            |
| IRCT20150808023559N20 | Iran      | 2020-Jul             | HOSP     | FPV + HCQ, HCQ + LPV/r                             | 100            |
| IRCT20200322046833N1  | Iran      | 2020-Apr             | HOSP     | HCQ + Antiretrovirals, HCQ + Antiretrovirals + Umifenovir | 100          |
| NCT04343092           | Iraq      | 2020-May             | HOSP     | HCQ + AZT, HCQ + AZT + Other                       | 100            |
| IRCT20200317046797N3  | Iran      | 2020-Jul             | HOSP     | HCQ + LPV/r + Antivirals, Igs + HCQ + LPV/r + Antivirals | 100          |
| IRCT20180725040596N2  | Iran      | 2020-Sep             | HOSP     | HCQ + LPV/r, HCQ + Umifenovir                      | 100            |
| IRCT20200418047126N1  | Iran      | 2020-Jun             | HOSP     | HCQ, HCQ + Colchicine                              | 100            |
| IRCT20190418043307N1  | Iran      | 2020-Jun             | HOSP     | HCQ, HCQ + Ivermectin                              | 100            |
| IRCT20200325046859N2  | Iran      | 2020-Jun             | HOSP     | HCQ, HCQ + Umifenovir                              | 100            |
| IRCT20080901001165N53 | Iran      | 2020-Aug             | HOSP     | IFN, SOC                                           | 100            |
| IRCT20151227025726N15 | Iran      | 2020-Jul             | HOSP     | LPV/r, Umifenovir                                  | 100            |
| IRCT20200324046850N1  | Iran      | 2020-Jul             | HOSP     | N-Acetyl-cysteine, SOC Vitamin D3, Vitamin D3 + N-Acetyl-cysteine | 100          |
| IRCT Number          | Country   | Start Date | Study Type | Intervention                                                                 | Subjects |
|---------------------|-----------|------------|------------|------------------------------------------------------------------------------|----------|
| IRCT20200525047562N1 | Iran      | 2020-Jul   | HOSP       | Plasma based therapy, SOC                                                     | 100      |
| IRCT20080901001165N58 | Iran      | 2020-Jun   | HOSP       | Plasma based therapy, SOC                                                     | 100      |
| IRCT20190727044343N2 | Iran      | 2020-Apr   | HOSP       | SOC, Statins                                                                 | 100      |
| NCT04288102         | China     | 2020-May   | HOSP       | SOC, Stem cells                                                              | 100      |
| NCT04363736         | United States | 2020-Aug  | HOSP       | TCZ                                                                         | 100      |
| IRCT20120225009124N4 | Iran      | 2020-Jun   | HOSP       | Corticosteroids + Igs + IFN, HCQ + Antivirals                               | 105      |
| IRCT20200402046923N1 | Iran      | 2020-May   | HOSP       | Alternative therapy, SOC                                                     | 110      |
| IRCT20200415047092N1 | Iran      | 2020-May   | HOSP       | AZT + Oseltamivir + LPV/r + Antiretroviral + HCQ, Oseltamivir + LPV/r + Antiretroviral + HCQ | 110      |
| IRCT20200411047025N1 | Iran      | 2020-May   | HOSP       | HCQ + Antiretroviral, HCQ + Antiretroviral + Vitamins                       | 110      |
| IRCT20171122037571N2 | Iran      | 2020-May   | HOSP       | Remdesivir + Chloroquine + LPV/r or Atazanavir                              | 120      |
| IRCT20200405046951N1 | Iran      | 2020-Aug   | HOSP       | SOC, Vitamin A                                                               | 120      |
| NCT04276688         | China     | 2020-Mar   | HOSP       | LPV/r, LPV/r + IFN                                                          | 127      |
| NCT044473170        | United Arab Emirates | 2020-May | HOSP       | SOC, Stem cells                                                             | 146      |
| IRCT20200316046792N1 | Iran      | 2020-May   | HOSP       | Alternative therapy, SOC                                                     | 150      |
| IRCT20200411047016N1 | Iran      | 2020-Jun   | HOSP       | Alternative therapy, SOC                                                     | 150      |
| IRCT20200705048013N1 | Iran      | 2020-Jul   | HOSP       | HCQ + Vitamins + Non-                                                        | 150      |
| Trial ID          | Country | Start Date | Study Type | Intervention                                      | Control | Patient Count |
|------------------|---------|------------|------------|--------------------------------------------------|---------|---------------|
| CHICTR2000029308 | China   | 2021-Jan   | HOSP       | invasive respiratory support + Plasma based therapy, Other |         |               |
| IRCT20200325046860N1 | Iran     | 2020-Aug | HOSP | LPV/r, SOC |         | 160           |
| IRCT20160310026998N11 | Iran     | 2020-Apr | HOSP | Conv plasma, SOC |         | 200           |
| IRCT20080901001165N46 | Iran     | 2020-Aug | HOSP | metformin, SOC |         | 200           |
| CHICTR2000030254 | China   | NA         | HOSP       | FPV, Umifenovir |         | 240           |
| NCT04323527    | Brazil  | 2020-May   | HOSP       | HCQ |         | 278           |
| IRCT20200318046812N1 | Iran     | 2020-Jun | HOSP | HCQ + FPV, HCQ + LPV/r |         | 324           |
| IRCT20160316027081N1 | Iran     | 2020-Apr | HOSP | licorice, SOC |         | 374           |
| NCT04327388    | Argentina | 2020-Jul | HOSP       | Sarilumab, SOC |         | 421           |
| NCT04321278    | Brazil  | 2020-Jun   | HOSP       | HCQ, HCQ + AZT |         | 440           |
| NCT04320615    | United States | 2020-Jun | HOSP       | SOC, TCZ |         | 450           |
| NCT04332991    | United States | 2020-Jun | HOSP       | HCQ, SOC |         | 479           |
| IRCT20200624047908N1 | Iran     | 2020-Sep | HOSP | DAA, SOC |         | 1000          |
| NCT04280705    | United States | 2020-May | HOSP       | Remdesivir, SOC |         | 1062          |
| NCT04292899    | United States | 2020-Apr | HOSP       | Remdesivir |         | 4891          |
| IRCT20200510047383N1 | Iran     | 2020-Aug | HOSP | SOC, TCZ |         | 100           |
| IRCT20200508047345N1 | Iran     | 2020-Jun | OUTPAT     | Alternative therapy |         | 100           |
| IRCT20200415047089N1 | Iran     | 2020-May | OUTPAT     | Alternative therapy, SOC |         | 100           |
| NCT04349241    | Egypt   | 2020-Jun   | OUTPAT     | FPV, SOC |         | 100           |
| IRCT20160313027033N2 | Iran     | 2020-May | OUTPAT     | Nutrition, SOC |         | 120           |
| NCT04483830    | Mexico  | 2020-Aug   | OUTPAT     | Anticoagulants, SOC |         | 243           |
| NCT04365738    | Turkey  | 2020-Apr   | OUTPAT     | Education, Non-invasive respiratory support |         | 270           |
| NCT04304053    | Spain   | 2020-Jun   | OUTPAT     | HCQ + Antivirals, SOC |         | 2300          |
| IRCT20160625028622N1 | Iran     | 2020-Apr | OUTPAT | Noscapine, SOC |         | 125           |
| NCT04337541    | Denmark | 2020-Jun   | PREV       | Surgical Face mask, SOC |         | 6000          |
| Study ID                  | Country   | Start Date | Status   | Treatment Details                                                                 |
|--------------------------|-----------|------------|----------|-----------------------------------------------------------------------------------|
| IRCT20200503047280N1     | Iran      | 2020-Jul   | PREV     | Alternative therapy, SOC                                                          |
| IRCT20190122042450N4     | Iran      | 2020-Jun   | PREV     | oral polio vaccine                                                                |
| IRCT20140428017469N1     | Iran      | 2020-Jul   | PREV     | HCQ, SOC                                                                         |
| NCT04308668              | United States | 2020-May | PREV     | HCQ, SOC                                                                         |
| NCT04392219              | United Kingdom   | 2020-Aug  | PREV     | EIDD-2801, SOC                                                                  |
| CHICTR2000034825         | China     | 2020-Dec   | PREV     | SOC, Inovio DNA plasmid vaccine                                                    |
| NCT04408456              | India     | 2020-Jul   | PREV     | HCQ, SOC                                                                         |
| CHICTR2000029479         | China     | 2020-May   | PREV     | SOC, TCM                                                                         |
| NCT04342650              | Brazil     | 2020-May   | PREV     | Chloroquine diphosphate, SOC                                                      |
| IRCT20171105037262N4     | Iran      | 2020-Jul   | UNCLEAR  | HCQ, HCQ + adalimumab                                                            |
| IRCT20200410047009N1     | Iran      | 2020-Jul   | UNCLEAR  | NSAIDs, SOC                                                                      |
| IRCT20200408046987N1     | Iran      | 2020-Jun   | UNCLEAR  | Ivermectin, SOC                                                                  |
| IRCT20200404046934N1     | Iran      | 2020-Apr   | UNCLEAR  | Alternative therapy, SOC                                                          |
| IRCT20180520039738N2     | Iran      | 2020-Apr   | UNCLEAR  | SOC, Vitamin A                                                                    |
| IRCT20131129015584N2     | Iran      | 2020-Jun   | UNCLEAR  | LPV/r + AZM, LPV/r + AZM + Alternative therapy                                   |
| CHICTR2000032165         | China     | 2021-Mar   | UNCLEAR  | Education, TCM + Education                                                       |
| CHICTR2000029434         | China     | 2020-Dec   | UNCLEAR  | SOC, TCM                                                                         |
| CHICTR2000029433         | China     | 2020-Dec   | UNCLEAR  | SOC, TCM                                                                         |
| NCT04530422              | Egypt     | 2020-Jul   | UNCLEAR  | DAA, Oseltamivir + HCQ + AZM                                                      |
| CHICTR2000029559         | China     | 2020-Feb   | UNCLEAR  | HCQ, SOC                                                                         |
| CHICTR2000029868         | China     | 2020-Jun   | UNCLEAR  | HCQ, SOC                                                                         |
| Registration ID   | Country       | Date     | Setting | Treatment                                                                 | Results |
|------------------|---------------|----------|---------|---------------------------------------------------------------------------|---------|
| NCT04523831      | Bangladesh    | 2020-Aug | UNCLEAR | Ivermectin + Antibiotics, SOC                                             | 400     |
| NCT04446104      | Singapore     | 2020-Aug | UNCLEAR | HCQ, Hygiene, Ivermectin, Vitamins, Vitamins + Zinc                       | 4257    |
| NCT04542694      | Russia        | 2020-Sep | HOSP    | Favipiravir                                                               | 200     |
| NCT04523831      | Bangladesh    | 2020-Oct | HOSP    | Ivermectin+doxycycline                                                   | 363     |
| NCT04425850      | Argentina     | 2020-Oct | OUTPAT  | Buccal ivermectin                                                         | 229     |
| NCT04425850      | Egypt         | 2020-Aug | OUTPAT  | Ivermectin                                                               | 404     |
| NCT04323592      | Italy         | 2020-June | HOSP    | Methylprednisolone                                                       | 173     |

**SUPPLEMENTARY TABLE 2: TRIALS COMPLETED AS OF December 27, 2020.** The registration ID for the respective regulatory body is given along with the country of registration and the date of completed enrolment. The setting for subjects in each trial: HOSP: Hospitalized; PREV: Healthy or exposed volunteers; OUTPAT: Infected patients, not hospitalized; UNCLEAR: Including multiple categories. SOC: Standard of Care; FPV: Favipiravir; LPV/R: lopanovir/ritonavir; HCQ: hydroxychloroquine; AZM: azithromycin; TCM: A Chinese herbal tea; NSAID: Non-steroidal anti-inflammatory drug; Conv Plasma: Convalescent plasma.