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Huge Global Push for RCTs in COVID-19: From Random to Randomized

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April 04, 2020

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Scientists and clinicians across the globe have responded to the ongoing coronavirus pandemic with a huge, high-quality global research effort to find a treatment for COVID-19.

As shown in the Table (see below) of all COVID-19 randomized controlled treatment trials, almost 60 of such trials are planned, recruiting, or underway.

This impressive roll-call of studies just 3 to 4 months after the COVID-19 outbreak is testament to the progress that has been made since the Ebola outbreak in 2014, said Andre Kalil, MD, MPH, of the University of Nebraska Medical Center in Omaha.

Kalil is leading the first clinical trial in the United States of an experimental treatment for COVID-19, the National Institutes of Health (NIH)-sponsored Adaptive COVID-19 Treatment Trial (ACTT).

"Years ago it could take months or years to design a randomized controlled trial," Kalil told *Medscape Medical News.* "We learned during the Ebola outbreak that we've got to do much better than that. With the COVID-19 outbreak, we were able to get a randomized trial up and running in a matter of weeks. It's a very optimistic message: we can do that really fast, efficiently, and safely."

Kalil emphasized the need for randomized controlled trials in a *JAMA* Viewpoint article published last month.

"Without a control group, we can never, ever safely find new medications for any disease," Kalil commented.

The problem with off-label use and compassionate use of drugs is interpretation of results. If the patient died, it's assumed he or she died of the disease, but if the patient survived, it's assumed he or she survived because of the given drug, but "this is not true," he said.

Kalil emphasized there is no way to know whether patients actually benefit from a drug or are harmed by it without a randomized clinical trial — a well-established principle of evidence-based medicine that can be forgotten during a crisis.

This tragedy of not discovering new therapies during an outbreak cannot be repeated. Dr Andre Kalil

Kalil cited the lesson of the 2014 Ebola outbreak, in which 30,000 individuals were infected and numerous therapies were tested, but no new drugs emerged, in part because virtually all studies were uncontrolled, single-arm endeavors. "This tragedy of not discovering new therapies during an outbreak cannot be repeated," he commented.

Canadian researchers drew similar conclusions from the extensive use of oseltamivir during the 2009 H1N1 pandemic. In a commentary in the *Canadian Medical Association Journal*, Matthew Cheng, MDCM, of McGill University Health Centre in Montreal, Canada, and colleagues wrote, "Even now, because there has been no RCT, it is not definitely known whether oseltamivir is efficacious…"

The Canadian authors conclude, "There is a strong ethical and clinical argument for replacing such 'random' care with randomized care."

Many of the larger studies are collaborative, multinational trials linking study initiators in the United States, Canada, China, and France with clinical researchers in Southeast Asia, Australasia, and a dozen European countries.

China is currently running more randomized treatment trials than any other country, closely followed by the United States. So far, most countries hit hard by COVID-19 are hosting at least one randomized study, with the exception of Spain and Iran. This will likely change over time — the World Health Organization (WHO) is working on a randomized, multicenter adaptive trial that will cover "multiple sites," so far unspecified.

WHO has identified a list of "promising candidates" for COVID-19 treatment. These include remdesivir (an investigational agent); lopinavir-ritonavir (approved for use in HIV) with or without interferon; investigational immunotherapies such as monoclonal and polyclonal antibodies; and convalescent sera.

In its January 27 statement, WHO did not support the antimalarial chloroquine (or hydroxychloroquine), ribavirin (used for hepatitis), or corticosteroids/steroids for COVID-19 clinical studies.

WHO is encouraging adaptive trial designs that test candidate drugs in sequence and can be launched quickly.

Four Multinational Trials Underway

Four COVID-19 multinational adaptive trials are already underway, one starting with the investigational agent remdesivir, and two with the HIV drug combination of lopinavir-ritonavir. The fourth has four therapy groups from the outset: remdesivir, lopinavir-ritonavir with or without interferon, and hydroxychloroquine.

Remdesivir is the first agent investigated in the NIH-sponsored trial ACTT, headed by Kalil at the University of Nebraska.

A broad-spectrum antiviral agent, remdesivir (GS-5734, Gilead Sciences Inc) has been studied as a potential treatment for Ebola, Marburg, MERS, and SARS without success. Kalil said remdesivir was chosen as the kick-off drug candidate for the NIH COVID-19 study on the basis of data from cell culture and two animal models.

(Two other single-country trials are studying remdesivir, one in mild/moderate patients and one in severe COVID-19. Both are supported by the Chinese Academy of Medical Sciences. The NIH took into account the Chinese study designs in the creation of ACTT, as well as

WHO's adaptive trial design.)

The first results on remdesivir are expected soon. The two Chinese studies aim to report first results as early as April, and Kalil said results of the ACTT trial will be available "within a few weeks."

Gilead Sciences, the developer of remdesivir, is in the process of making the drug available under expanded access instead of unwieldy, individual compassionate-use requests, to cope with "overwhelming demand." After a global outcry, it also recently rescinded its request for orphan drug designation for remdesivir, which would have granted the company market exclusivity for 7 years.

The two other multinational adaptive studies are starting with lopinavir-ritonavir, a protease-inhibitor combination indicated for HIV/AIDS prevention and treatment. In combination with interferon B, it has shown effectiveness against another coronavirus, MERS, in animal models. However, results of lopinavir-ritonavir against COVID-19 have thus far been disappointing.

In North America, the study of lopinavir-ritonavir is being spearheaded by Canada with two trials. The Canadian-driven adaptive CATCO trial is the largest treatment study in the country and is part of WHO's solidarity protocol for hospitalized patients. After lopinavir-ritonavir, the multinational team plans to look at hydroxychloroquine and remdesivir.

The other Canadian adaptive trial of lopinavir-ritonavir is REMAP-CAP, a study of community-acquired pneumonia that was already running and has now folded in COVID-19 patients not in the CATCO study.

The first results of these Canadian-run trials could be available as early as May.

The fourth large trial is a European adaptive treatment trial. The DisCoVeRy trial has four parallel therapy groups and is testing lopinavir-ritonavir, either with or without interferon, against remdesivir and hydroxychloroquine.

Other antivirals being tested against COVID-19 are arbidol, darunavir, favipiravir, oseltamivir, and various protease-inhibitor combinations in trials in China and Thailand. The WHO has just launched the SOLIDARITY trial, a randomized, multicenter, adaptive trial of antivirals currently involving 45 countries, and counting.

Other therapies recommended by WHO for further investigation include monoclonal antibodies and other investigational immunotherapies. There has been intense interest in the use of interleukin-6 inhibitors, for example tocilizumab (*Actemra*, Genentech), for use in cytokine release storm in COVID-19 pneumonia, which is similar to use of these agents after CAR T-cell therapy. A total of 10 randomized clinical trials of these products against COVID-19 are currently running, spanning the United States, Canada, China, and Europe.

Convalescent plasma is also recommended for further investigation by WHO, and studies are ongoing. The US Food and Drug Administration approved emergency use of convalescent plasma for seriously ill COVID-19 patients on March 28.

Hydroxychloroquine and Chloroquine

Despite enthusiastic endorsement by President Trump after reports of positive results from an open-label French study, hydroxychloroquine and chloroquine are not currently recommended for further investigation in COVID-19 by WHO.

Two COVID-19 randomized clinical trials with hydroxychloroquine have reported results, both from China. A study of 30 patients with early COVID-19 treated in the Shanghai Public Health Center, published in February, found that hydroxychloroquine 400 mg per day was no more effective than standard care. Using the same dose in a similar patient population, a non-peer-reviewed trial of 62 patients at the Renmin Hospital in Wuhan, posted on April 2, found that hydroxychloroquine reduced the time to clinical recovery.

Five large hydroxychloroquine randomized controlled trials with sites in Canada, the United States, China, Europe, and Brazil — aiming for 8000 patients — are currently in the works.

Despite the controversies, the overwhelming international collaborative effort in COVID-19 science is cause for hope, said Kalil, who has no financial conflicts of interest.

"My hope is that we're going to find a way to slow down and stop outbreaks for the future," Kalil said. If one looks at the many trials by researchers from multiple countries, "I think it shows that once all of us combine efforts, we can find solutions fast, save lives, and be better prepared for future outbreaks."

Tracking the Trials

Several groups are tracking clinical trials of both therapeutics and vaccines for COVID-19, including the Milken Institute COVID-19 tracker, the Oxford Trials Tracker on COVID-19, and the Centre for Evidence-Based Medicine (CEBM) COVID-19 Registered Trials Tracker.

Medscape has compiled a table (see below) of 50+ randomized clinical trials of treatments for COVID-19 that are currently ongoing and planned, with estimated completion dates. (Data sources include clinicaltrials.gov, WHO R&D Blueprint, and news feeds. Data are current as of April 3.)

Table. COVID-19 RCTs

Therapy	Trial Name	Proposed # of Patients	Participating Countries	Primary Completion Date
Remdesivir RCTs				
Remdesivir	Mild/Moderate 2019-nCoV Remdesivir RCT	308	China	April 10, 2020
Remdesivir	Severe 2019-nCoV Remdesivir RCT	453	China	April 3, 2020
Remdesivir	Study to Evaluate the Safety and Antiviral Activity of	600	US, Hong Kong,	May 1,

	Remdesivir (GS-5734) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment		South Korea, Singapore, Taiwan	2020
Remdesivir	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19)	400	US, Hong Kong, South Korea, Singapore, Taiwan	May 1, 2020
Remdesivir	Adaptive COVID-19 Treatment Trial (ACTT) (NIH supported)	440	US, Japan, South Korea, Singapore	April 1, 2023
Remdesivir, lopinavir-ritonavir, interferon, hydroxychloroquine	DisCoVeRy: Trial of Treatments for COVID-19 in Hospitalized Adults	3100	France	March 1, 2023
Lopinavir/Ritonavir RCTs				
Lopinavir-ritonavir, anakinra, macrolides, corticosteroids, interferon	REMAP-CAP: A randomised, embedded, multi-factorial, adaptive platform trial for community-acquired pneumonia	No maximum	Canada and 13 other countries (Australia, NZ, UK, "a dozen EU countries"), 50 sites	End April/Early May 2020
Lopinavir-ritonavir, hydroxychloroquine	Comparison of lopinavir-ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	150	South Korea	May 1, 2020
Lopinavir-ritonavir, hydroxychloroquine, remdesivir	CATCO: Canadian Treatments for COVID-19 trial - Canadian Arm of the WHO SOLIDARITY trial	440	Canada plus 45 countries so far	March 18, 2022
Lopinavir-ritonavir, interferon, Chinese medicine	Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection	150	China	January 22, 2021
Lopinavir-ritonavir, oseltamivir, arbidol hydrochloride	A Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia	400	China	June 1, 2020
Lopinavir-ritonavir, ribavirin, interferon	Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	70	Hong Kong	January 31, 2022
Remdesivir, lopinavir-ritonavir, interferon, hydroxychloroquine	DisCoVeRy: Trial of Treatments for COVID-19 in Hospitalized Adults	3100	France, Belgium, German, the Netherlands, Spain, Sweden, UK	March 1, 2023

Lopinavir-ritonavir	A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19	199	China	February 3, 2020
Lopinavir-ritonavir	CORIPREV-LR: COVID-19 Ring-based Prevention Trial With Lopinavir-Ritonavir	1220	Canada	March 31, 2021
Other Antiviral RCTs				
Arbidol (antiviral), bromhexine hydrochloride (mucolytic), interferon	Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19)	60	China	April 15, 2020
Darunavir, cobicistat	DACO-nCoV: Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV	30	China	August 31, 2020
Favipiravir, oseltamivir, protease-inhibitor combinations	THDMS-COVID19: Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19: A Randomized Control Trial (THDMS-COVID19)	80	Thailand	October 31, 2020
Investigational Immunotherapy RCTs				
Lopinavir-ritonavir, anakinra, macrolides, corticosteroids, interferon	REMAP-CAP: A randomised, embedded, multi-factorial, adaptive platform trial for community-acquired pneumonia	No maximum	Canada and 13 other countries (Australia, NZ, UK, "a dozen EU countries"), 50 sites	End April/Early May 2020
Bevacizumab	BEST-RCT: Bevacizumab in Severe or Critically Severe Patients With COVID-19 Pneumonia-RCT	118	China	June 30, 2020
Emapalumab, anakinra	Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection.	54	Italy	July 1, 2020
CD24Fc	SAC-COVID: CD24Fc as a Non-antiviral Immunomodulator in COVID-19 Treatment	230	US	May 1, 2021
Tocilizumab, favipiravir	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	150	China	May 1, 2020
"PD-1 blocking antibody", thymosin	Immunoregulatory Therapy for 2019-nCoV	120	China	April 30, 2020
Sarilumab	CORIMUNO-19 - SARI: Cohort Multiple Randomized	180	France	March 26,

	Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Sarilumab Trial -			2021
Sarilumab	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	400	US	March 16, 2021
ASC09F, ritonavir, oseltamivir	A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia	60	China	May 1, 2020
Tocilizumab	COVACTA: A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia	330	US	August 31, 2021
Tocilizumab, sarilumab	TOCIVID: Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure	200	Denmark	June 1, 2021
Human Product RCTs				
Convalescent plasma	CSSC-OO1: Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19	150	US	December 31, 2022
Stem cells	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	48	China	June 30, 2020
Stem cells	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	90	China	December 31, 2020
Natural-killer cells	NK Cells Treatment for Novel Coronavirus Pneumonia	30	China	September 30, 2020
Vitamin C RCTs				
Vitamin C (high-dose IV)	LOVIT: Lessening Organ Dysfunction With VITamin C	800	Canada	December 31, 2021
Vitamin C (high-dose IV)	Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	140	China	September 30, 2020
(Hydroxy)Chloroquine RCTs				
Chloroquine, azithromycin	ACT COVID19: Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial	1500	Canada "+ international"	September 30, 2020
Hydroxychloroquine	COVID-19 PEP: Post-Exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	3000	Canada, US	April 21, 2020
Hydroxychloroquine	Efficacy and Safety of Hydroxychloroquine for Treatment of	30	China	February

	Pneumonia Caused by 2019-nCoV (HC-nCoV)			25, 2020
Hydroxychloroquine	Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial	62	China	February 28, 2020
Hydroxychloroquine	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19) [includes treatment of early symptoms]	1600	US	March 1, 2021
Hydroxychloroquine, azithromycin	Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II)	440	Brazil	August 30, 2020
Other RCTs				
Chinese medicine	Yinhu Qingwen Decoction for the Treatment of Mild/Common CoVID-19	300	China	January 1, 2021
Chinese medicine	Yinhu Qingwen Granula for the Treatment of Severe CoVID-19	116	China	March 30, 2021
Chinese medicine, N-acetylcysteine (cysteine supplement)	Treatment of Pulmonary Fibrosis Due to 2019-nCoV Pneumonia With Fuzheng Huayu	136	China	December 1, 2022
Colchicine	COLCORONA: Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)	6000	Canada	September 1, 2020
Immunoglobulin	The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia	80	China	April 30, 2020
Interferon, arbidol hydrochloride	A Prospective/Retrospective, Randomized Controlled Clinical Study of Interferon Atomization in the 2019-nCoV Pneumonia	100	China	June 1, 2020
Losartan	Losartan for Patients With COVID-19 Not Requiring Hospitalization	516	US	April 1, 2021
Losartan	Losartan for Patients With COVID-19 Requiring Hospitalization	200	US	April 1, 2021
Methylprednisolone	Steroids-SARI: Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure	80	China	April 25, 2020
Methylprednisolone	The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia	100	China	June 1, 2020
Methylprednisolone	Efficacy and Safety of Corticosteroids in COVID-19	400	China	May 1,

				2020
Nitric oxide gas	NoCovid: Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19	240	US, China, Italy	April 1, 2021
Nitric oxide gas	NOSARSCOVID: Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19	200	US, China, Italy	March 21, 2021
PUL-042 inhalation solution	PUL-042 Inhalation Solution to Reduce the Severity of COVID-19 in Adults Positive for SARS-CoV-2 Infection	100	US	September 1, 2020
Tetrandrine	TT-NPC: Tetrandrine Tablets Used in the Treatment of COVID-19	60	China	March 1, 2021

Cite this: Huge Global Push for RCTs in COVID-19:From Random to Randomized - *Medscape* - Apr 04, 2020.