Supplemental Online Content

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eMethods.

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Methods Overview

Since the goal of this study was to cast the widest net possible in identification of Covid-19 clinical trials, we reviewed all active or planned clinical trials indexed in www.clinicaltrials.gov that were specifically intended for prevention or treatment of Covid-19. Because of the expedited nature of most current trials and the multiple phases included in many indexed trials, we opted to review all trials in all phases simultaneously. We conducted a separate sub-analysis of Phase III trials, which are intended to include a broad target population for evaluating the treatment. Finally, we conducted a specific sub-analysis of vaccine trials to evaluate their potential age-related exclusions.

Clinical trial selection

The selection of clinical trials for this study is described in **Appendix Figure 1**. Planned or active clinical trials for Covid-19 were identified by keyword *Covid-19* and synonyms: *SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, 2019-nCOV, 2019 novel coronavirus,* and *Wuhan coronavirus* from October 1, 2019 to June 1, 2020 inclusive. We then excluded studies classified as observational or expanded access studies, yielding 1,072 clinical trials for Covid-19. The entries for these trials were reviewed, and we excluded studies which were not directed towards prevention or treatment of Covid-19 related infection (e.g., studies for relief of anxiety or cessation of smoking), study populations that were exclusively healthcare workers or pregnant women, pediatric (age <18 years) studies, and studies that were suspended or

withdrawn. Thus, the final sample included 847 clinical trials (detailed in **Appendix Table 1**), providing the context for our subsequent analyses.

Data abstraction

Each www.clinicaltrials.gov entry was abstracted by at least one trained research associate. All researchers were cross-trained, and information was abstracted in a standardized manner, with twice weekly group sessions to assure standardization. The following information was abstracted for each study: Clinical Trials database identification number, site(s) location by country, interventions, outcome measures, age, study phase, enrollment number, date first posted to the database, and unique study URL. Age exclusions were identified by viewing all portions of the eligibility criteria, including ages eligible for study, inclusion criteria, and exclusion criteria. Specific age exclusions were classified into 5-year categories as follows: >55 or ≥55, >60 or ≥60, >65 or ≥65, >70 or ≥70, >75 or ≥75, >80 or ≥80 years of age. We were most interested in exclusions of the 65-80 year olds, the group most at risk from Covid-19. Because of high risk for comorbidity, specific exclusion of age 80 and older categories were not counted as exclusions for this study.

For all entries, we further abstracted indirect age-related exclusions which may preferentially affect older adults and which were not well-justified. These included broad, poorly specified exclusions that were left to the trial investigators' subjective judgment (e.g., one study excluded: "any condition that the investigator considers ineligible for clinical trials"). We identified exclusions for specific comorbidities which are common in older adults and where severity or degree was not specified (e.g., any hypertension, any diabetes, anemia non-specified). While severe or unstable illnesses were considered justified exclusions, many trials listed exclusion for common comorbidities with no severity level specified. We categorized studies which indicated non-specified 'concerns about compliance with follow-up' as an exclusionary criterion. We

ascertained studies that excluded for non-specified cognitive impairment or any difficulty following instructions, and those that did not allow for any proxy consent. Finally, the requirement for use of and facility with information technology (e.g., wireless internet, smartphone, text messaging, or webcam) was determined, since these requirements may preferentially exclude many older adults. Other reasons for exclusion that were not well-justified were identified, such as residing in a long-term care facility, and non-specified hearing or vision impairment.

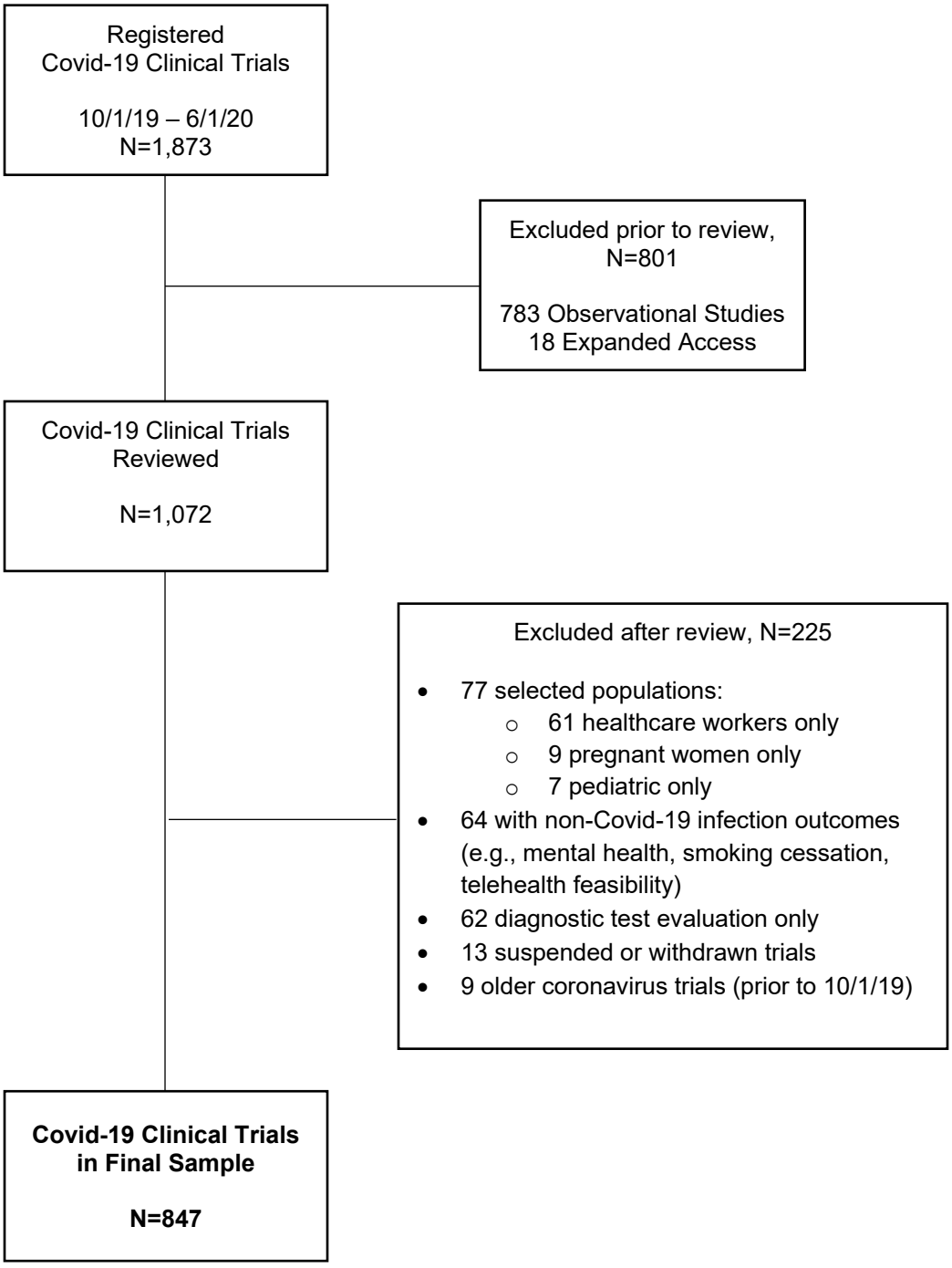
Recheck and adjudication of abstractions

All of the potential age-related exclusions were independently rechecked and adjudicated by two clinicians; if either clinician considered the exclusion justifiable for any reason, it was not counted in the results. In addition, one in ten of the entries (10% subsample) underwent a comprehensive second blinded abstraction by an independent trained rater. The few minor discrepancies identified were resolved in a consensus conference with a clinical expert who did not participate in the extraction process.

Categorization of treatments

All interventions and treatments were grouped into related categories by two medically trained clinicians. For studies with multiple treatments, a single primary intervention was selected for purposes of study classification. A complete listing of all the interventions and treatments within each category is provided in **Appendix Table 2**.

Appendix Figure 1. Clinical Trial Selection Process



Appendix Table 1. Description of included COVID-19 clinical trials, N=847

Sample size		**N (%)**
	< 50	205 (24%)
	50-99	147 (17%)
	100-249	227 (27%)
	250-499	110 (13%)
	500-999	75 (9%)
	≥ 1000	77 (9%)
	Not Indicated	6 (1%)
Continent of origin		**N (%)**
	North America	312 (37%)
	Europe	263 (31%)
	Asia	167 (20%)
	Africa	37 (4%)
	South America	37 (4%)
	Australia	5 (1%)
	Multiple	26 (3%)
Trial phase(s) included		**N (%)**
	Phase I	64 (8%)
	Phase I & Phase II	50 (6%)
	Phase II	270 (32%)
	Phase II & Phase III	77 (9%)
	Phase III	155 (18%)
	Phase IV	57 (7%)
	Not Applicable	174 (20%)
Month trial posted		**N (%)**
	October 2019-January 2020	2 (<1%)
	February 2020	38 (4%)
	March 2020	91 (11%)
	April 2020	405 (48%)
	May 2020	298 (35%)
	June 1, 2020	13 (2%)

Appendix Table 2. All specific COVID-19 interventions by treatment categories (alphabetical order)

Antibiotics: Azithromycin, BCG Vaccine, Carrimycin, Clarithromycin, Doxycycline, Trimethoprim/Sulfamethoxazole

Anticoagulant: Alteplase, Argatroban, Aspirin, Clopidogrel, Defibrotide, Dipyridamole, Enoxaparin, Fondariniux, Heparin, Lithium heparinate, Nafamostat mesylate, tissue-Plasminogen Activator, Rivaroxaban, Unfractionated heparin

Antihypertensive: ACE inhibitor, Amlodipine, Angiotensin receptor blocker, Captopril, Hydrochlorothiazide, Losartan, non-RAS blocking antihypertensives, Prazosin, Ramipril, Recombinant bacterial ACE2 receptors-like enzyme of B38-CAP (rbACE2), Recombinant human angiotensin-converting enzyme 2 (rhACE2), Spironolactone, Telmisartan, Valsartan, Verapamil

Anti-inflammatory: ABX464, Alpha one antitrypsin inhalation, AT-001, Aviptadil, CM4620, Injectable Emulsion, Colchicine, Defibrotide, Desferal, Ibuprofen, Indomethacin, Inhaled, hypertonic ibuprofen, Ketamine, LSALT peptide, Methotrexate, Naltrexone, Naproxen, NP-120 (Ifenprodil), Piclidenoson, RPH-104, Vazegepant (BHV-3500), XPro1595

Antiparasitic: Artemisinin/Artesunate, Ivermectin, Ivermectin and Nitazoxanide, Levamisole and Isoprinosine, Niclosamide, Nitazoxanide

Antiseptic: 0.12% Chlorhexidine oral/nasal rinse, 0.5% Povidone/iodine oral/nasal rinse, CloSYS mouthwash, Crest Pro-Health Multi-Protection mouthwash, Daily room disinfection, Mouthrinse with beta-cyclodextrin and citrox, Methylene Blue, Oral-B Mouth Sore mouthwash, Povidone-iodine, Povidone-iodine nasal spray and gargle, ResCure™

Antiviral: Arbidol hydrochloride, ASC09/Ritonavir, AT-527, BLD-2660, Camostat mesylate, Clevudine, COVID-19 Specific T Cell derived exosomes (CSTC-Exo), Danoprevir and Ritonavir, Darunavir and Cobicistat, Darunavir and Ritonavir plus Oseltamivir, DAS181, EIDD-2801, Favipiravir, Favipiravir and Lopinavir/Ritonavir, LB1148, Lopinavir/Ritonavir, Lopinavir/Ritonavir combined with Xiyanping injection, Lopinavir and Ritonavir plus Oseltamivir, Oseltamivir, Partially HLA-matched Virus Specific T cells (VSTs), Remdesivir, Ribavirin, Umifenovir, Viral Specific T-cells (VSTs), Virazole

Blood product: Angiotensin peptide (1-7) derived plasma, Anti-SARS-CoV-2 Plasma, Anti-COVID-19 human immunoglobulin, Blood and derivatives, Blood plasma, CytoSorb-Therapy, Dialyzable Leukocyte Extract, Exchange blood transfusion from normal donor, High-titer anti-Sars-CoV-2 plasma, Human immunoglobulin, Hyper immunoglobulins containing anti-Corona, VS2 immunoglobulin, Hyperimmune plasma, IgIV, Octagam 10%, Ozone auto-hemotherapy, Plasma exchange, Plasma hyperimmune, Platelet rich plasma (active comparator), Recombinant human plasma gelsolin (Rhu-pGSN), SARS-CoV-2 non-immune Plasma, γ-Globulin

Device: Bidirectional oxygenation mouthpiece, Biosensors, CELLECTRA® 2000, Centricyte 1000, COViage, COVID-19 barrier box, COVSurf Drug Delivery System, Direct laryngoscopy, ECCO2R, Electric pad for human external pain therapy, Emergency Ventilator Splitter, Expiratory training device, Flow controlled ventilation (Evone-ventilator), gammaCore® Sapphire (non-invasive vagus nerve stimulator), GO2 PEEP MOUTHPIECE, Helmet Continuous Positive

Airway Pressure (CPAP), Helmet CPAP, HFNC, High flow nasal cannula, Home Pulse Oximetry Monitoring, Hyperbaric Chamber, Hyperbaric oxygen therapy, Inspiratory training device, Intraosseous access, Intravenous access, Kerecis Oral and Nasal Spray, Marker Therapeutics D2000 Cartridge (D2000) for use with the Spectra OptiaÂ® Apheresis System (Optia SPD Protocol), Mechanical ventilation with the automated BVM compressor, MLS Laser, NIO® (Intraosseous access), Normobaric oxygen therapy, Patient Status Engine, Premier Biotech COVID-19 IgG/IgM Rapid test Cassette, Robotic therapy, SCD, SLEDD with a L-MOD SYMBICORT RAPIHALER, TCC-COVID mHealth solution, The standard Macintosh laryngoscope, The Vie Scope laryngoscope, V/Q Vest

Immunomodulatory: Acalabrutinib, ACE2 CAR-NK cells, Allogeneic NK transfer, AMY-101, Anakinra, Anakinra and Ruxolitinib, APL-9, Avdoralimab, AVM0703, Azoximer bromide, Baricitinib, Bevacizumab, BMS-986253, Canakinumab, CD24Fc, Clazakizumab, Cyclosporine, Cytokine Adsorption, Deferoxamine, DFV890, Duvelisib and Peripheral blood draw, EB05, Eculizumab, EDP1815, Emapalumab, Fingolimod, Garadacimab, Factor XIIa Antagonist, Monoclonal Antibody, Gimsilumab, Ibrutinib, IC14, IFX-1, IL15-NK cells, ILT101, Imatinib, IMU-838, Interferon Beta-1A, Interferon Beta-1B, Interferon-Alpha-2B, Interferon-Beta, Interleukin-7, Kevzara, Leflunomide, Lenalidomide, Lenzilumab, Leronlimab, Levilimab, LY3127804, MAS825, Mavrilimumab, Meplazumab, Metenkefalin and Tridecactide, MRx-4DP0004, MSTT1041A, N-803, Nintedanib, Nivolumab, NK cells, NKG2D CAR-NK cells, NKG2D-ACE2 CAR-NK cells, Olokizumab, Otilimab, Ozanimod, Pacritinib, PD-1 blocking antibody, Peginterferon Lambda-1A, Pembrolizumab (MK-3475), Ravulizumab, RBT-9, Recombinant human interferon α1β, Recombinant Human Interferon α2b, Recombinant Interferon Alfa-2b and Rintatolimod, RoActemra, RTB101, Ruxolitinib, Sargramostim, Sarilumab, Secukinumab [COSENTYX], Siltuximab, Sirolimus, Sirukumab, Tacrolimus, TD-0903, Thalidomide, TJ003234, Tocilizumab, Tofacitinib, Tradipitant, TXA127, Ulinastatin, UTTR1147A, Zanubrutinib, Zilucoplan®

Multimodal: Abidol Hydrochloride and Interferon atomization; Anakinra plus oSOC; ASC09F plus Oseltamivir; Atovaquone and Azithromycin; Azithromycin and Hydroxychloroquine; BAT + Calcifediol; Bromhexine +/- Hydroxychloroquine; Colchicine and Herbal phenolic monoterpene fractions; Combined use of a respiratory broad panel multiplex PCR and procalcitonin; Dapagliflozin and Ambrisentan; Darunavir/Ritonavir, Oseltamivir and Chloroquine; Hydroxychloroquine and Clindamycin; Hydroxychloroquine, Clindamycin and Primaquine; Favipiravir and Hydroxychloroquine; Favipiravir and Tocilizumab; Ganovo and Ritonavir +/- Interferon nebulization; Hydroxychloroquine and Sirolimus; Hydroxychloroquine and Ivermectin; Hydroxychloroquine and Radiation therapy; Hydroxychloroquine and Nitazoxanide; Hydroxychloroquine Sulfate and Lopinavir/ Ritonavir; Hydroxychloroquine, Azithromycin and Zinc Sulfate; Hydroxychloroquine, Azithromycin, Zinc Citrate, Vitamin D3, Vitamin B12 (active comparator); Hydroxychloroquine, Doxycycline; Hydroxychloroquine, Lopinavir/Ritonavir or Azithromycin and Placebo; Hydroxychloroquine, Zinc Sulfate and Doxycycline; Isotretinoin and Tamoxifen; Ivermectin and Chloroquine; Ivermectin and Doxycycline; Ivermectin, Azithromycin and Cholecalciferol; Levamisole, Budesonide and Formoterol; Lopoinavir/Ritonavir/Arbidol/Chloroquine phosphate; MCN (Methylene blue, vitamin C, N-acetyl cysteine); Merimepodib and Remdesivir; Niclosamide and Telehealth monitoring; Nitazoxanide and Azithromycin; Nitazoxanide, Ivermectin and Azithromycin; Nitazoxanide, Ribavirin and Ivermectin; Oseltamivir and Chloroquine; Oseltamivir, hormones and oxygen therapy; Oseltamivir, hormones, oxygen therapy and mesenchymal stem cells; oxygen therapy/alpha interferon/lopinavir/ritonavir; PUL-042 Inhalation Solution; Remdesivir and Baricitinib; Remdesivir and Tocilizumab; Resveratrol and Vitamin D3; Ritonavir and Oseltamivir; Ruxolitinib and simvastatin; SnPP Protoporphyrin plus Sunlight exposure; Sulfonatoporphyrin(TPPS) plus Sunlight exposure; Tirofiban, Clopidogrel, Acetylsalicylic acid and Fondaparinux; Tofacitinib and

Hydroxychloroquine; Vitamin C, Hydroxychloroquine, Azithromycin, Zinc Citrate, Vitamin D3, Vitamin B12; Wharton's jelly derived Mesenchymal stem cells and Hydroxychloroquine, lopinavir/ritonavir or azithromycin and placebo (standard therapy)

Non-pharmacologic: 100 cGy bilateral lung irradiation, 100 cGy single lung irradiation, Active PBMT/sMF, Auricular neuromodulation, Basic Body Awareness Therapy, Blood draw, Digital cardiac counseling, Double-trunk mask, GammaCore® (Vagus nerve stimulation), High intensity interval training group, Homecare monitoring, HOME-CoV rule implementation, Intervention program, Low dose radiation therapy, Lung impedance technique, Mechanical ventilation, Medical Ozone procedure, Medically tailored meals, Neuromuscular Electrical Stimulation, Olfactory retraining, Olfactory retraining and Corticosteroid nasal irrigation, Ophthalmologic exam, Phone-call screening and management by a medical student/general practitioner tandem, Physiotherapy, Physiotherapy (chest) using a non-invasive oscillating device, Prayer, Psychological treatment, PT-Pal, Pulmonary and Motor Rehabilitation, Pulmonary physiotherapy, Rehabilitation, Self-guided exercises, Self-management booklet (SWitCh: Stay well during COVID-19), Single fraction whole lung radiotherapy, Stellate Ganglion Block, Surgical facial mask, Telerehabilitation, Telerehabilitation based yoga and mindfulness, The PREPARE program, Therapy Intervention, Transcutaneous auricular vagus nerve stimulation, Ultra-low-dose radiotherapy, Video based exercise, Yoga and High intensity interval training group

Nutraceutical: Acacia Senegal, Açaí palm berry extract, Aerosolized 13 cis retinoic acid, Aerosolized All trans retinoic acid, Anluohuaxian, ArtemiC, Ascorbic Acid, Ascorbic Acid and Zinc Gluconate, Ayurveda, Azinc, Chinese medicine treatment, Cholecalciferol, Dietary Supplement containing resistant starch, Escin, Essential oils, Folic Acid, Glucose tablets, Honey, Nigella Sativa / Black Cumin, Huaier Granule, Isocaloric/Isonutrigenous ONS, Isotretinoin (13 cis retinoic acid), Ketogenic diet, L-citrulline, Lactobaciltus rhamnosus GG, LEAF-4L6715, LEAF-4L7520, , Moxibustion plus Cupping, NaCl 0.9%, Natural honey, Nicotinamide riboside, Nigella sativa, Oral nutrition supplement (ONS) enriched in eicosapentaenoic acid, gamma-linolenic acid and antioxidants, P2Et (Caesalpinia spinosa extract), Probiotic, Quercetin, Saline Nasal Irrigation|Other: Saline with Baby Shampoo Nasal Irrigation, Silymarin, SivoMixx, Sodium Bicarbonate, Sodium Nitrite, T89, Tetrandrine Traditional Chinese Medicine Prescription, Vitamin Super B-Complex, Viusid and Asbrip, YinHu QingWen Decoction, Yinhu Qingwen Granula, Zinc Gluconate, Zinc Sulfate

Other pharmacologic treatments with under 9 drugs per category (categories): Antidiabetic, ECMO, Hormone, inhaled corticosteroid and/or bronchodilator, mucolytic

Other pharmacologic treatments (specific treatments): Almitrine, Atorvastatin, Bactek-R, Bicalutamide, Bovine Lipid Extract Surfactant, Bromhexine Hydrochloride, Budesonide and Formoterol, Budesonide Nasal, Candesartan, Chlorpromazine Injection, Chlorpromazine, Ciclesonide Metered Dose Inhaler [Alvesco], cSVF In Sterile Normal Saline, Dalargin, Dapagliflozin, Degarelix, DeltaRex-G, Dornase Alfa, ECMO, Inhalation Solution (Pulmozyme), Eicosapentaenoic acid gastro-resistant capsules, Estradiol patch, Etoposide, Fluoxetine, Fluvoxamine, Human Amniotic Fluid, Human cord tissue, mesenchymal stromal cells, Inhaled budesonide, Insulin regimen, Famotidine, Linagliptin, Lucinactant, Melatonin, Melphalan, Mesenchymal Stromal Cells, Microcannula Harvest Adipose, Derived tissue stromal vascular fraction (tSVF), Montelukast, Mycobacterium, N-acetylcysteine, N-acetylcysteine+ Fuzheng Huayu, Omeprazole, Organicell Flow, Oxytocin, Paracetamol, Plitidepsin, Poractant alfa, Progesterone, Propofol, Pulmozyme, Pyridostigmine Bromide, rhDNase I, Selinexor,

Sevoflurane, Sildenafil citrate, Simvastatin, Sitagliptin, T3 solution for injection, Thymosin, Tranexamic acid, Veru-111, Washed microbiota transplantation

Oxygen: Alveolar recruitment, CPAP treatment, Gas exchanges at different PEEP, Hemodynamics changes at different PEEP, High Flow Nasal Oxygen (HFNO), Hydrogen Oxygen Generator with Nebulizer, Hyperbaric Oxygen Therapy, Hypoxia : 14.3 and 12.7% FIO2, hypercapnia 7% CO2, inspiratory mechanical constraint, Inhaled Supplemental Oxygen, Lung mechanics at different PEEP, Oxygen therapy, Oxygen-ozone therapy, probiotic supplementation, Protective ventilation, Systemic indirect endovenous ozone therapy

Stem cells: ACT-20-CM, ACT-20-MSC, Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells, Allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC), Allogenic pooled olfactory mucosa-derived mesenchymal stem cells|Other: Standard treatment according to the Clinical protocols, Autologous adipose MSC, BM-Allo.MSC, BM-MSC, CAStem, Cord blood stem cells, CYNK-001, Dental pulp mesenchymal stem cells, FT516, HB-adMSC, Liberase Enzyme, MSCs-derived exosomes, MultiStem, NestaCell®, PLX-PAD, Remestemcel-L, Saline containing 1% Human serum albumin（solution of MSC, Stem Cell Educator, Treated Mononuclear Cells Apheresis, Umbilical cord Wharton's jelly-derived human stem cells, Umbilical cord-derived mesenchymal stem cells (UC-MSCs), XCEL-UMC-BETA

Steroid: Ciclesonide, Corticosteroid, Dexamethasone, Dexmedetomidine, Hydrocortisone, Hydrocortisone and Sodium Chloride 9mg/mL, Methylpredisolone, Methylprednisolone Sodium, Succinate, Prednisone

Vaccine: bacTRL-Spike; BNT162a1; BNT162a1, BNT162b1, BNT162b2, and BNT162c2; BNT162b1; BNT162b2; BNT162c2; ChAdOx1 nCoV-19; ChAdOx1 nCoV-19 boost; Inactivated SARS-CoV-2 vaccine; INO-4800; LV-SMENP-DC vaccine and antigen-specific CTLs; MenACWY; MenACWY vaccine and Boost; mRNA-1273; Pathogen-specific aAPC; Recombinant novel coronavirus vaccine (Adenovirus type 5 vector); SARS-CoV-2 vaccine; SARS-CoV-2 rS and Matrix-M Adjuvant; SCB-2019; SCB-2019 with AS03 adjuvant; SCB-2019 with CpG 1018 adjuvant plus Alum adjuvant; V-SARS