Regulation of in vitro diagnostics, therapeutics, and vaccines
WHO Update – 7
Coronavirus disease 2019 (COVID-19)
01 May 2020

World Health Organization

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Key Message

Three months after COVID-19 was declared a global public health emergency – WHO's highest level of alarm – the Emergency Committee reconvened on 30 April to evaluate the evolution of the pandemic, and to advise on updated recommendations.

On 24 April, WHO, together with global health actors, private sector partners and other stakeholders launched the Access To COVID-19 Tools (ACT) Accelerator, a global collaboration to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines.

The mission of the ACT Accelerator is not only accelerated development and availability of new COVID-19 tools, it is to accelerate equitable global access to safe, quality, effective, and affordable COVID-19 diagnostics, therapeutics and vaccines, and thus to ensure that in the fight against COVID-19, no one is left behind. A European rolling pledging campaign will start on 4 May 2020 to accelerate achievement of the objectives of this global collaboration.

Remdesivir, previously tested as an Ebola treatment, has generated promising results for the Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS), which are also caused by coronaviruses, suggesting it may have some effect in patients with COVID-19. Results of clinical trials in several countries are anticipated in the coming days.

Highlights and main issues

- An ethical framework for setting priorities for the allocation of resources during times of scarcity, including access to ventilators, vaccines and medicines has been published.
- WHO advice provided on monitoring quality, safety and performance of IVDs.
- Links to a living synthesis of Covid-19 study results for candidate therapeutics published.
- Regulatory approval for the SOLIDARITY clinical trial has been obtained in 25 countries.
- The most commonly reported Adverse Drug Reactions for candidate therapeutics included in the SOLIDARITY trial continue to be those included in available product labelling.
- 8 vaccine candidates are now in clinical trials, with two in phase 2 trials.
- Communications on regulatory flexibilities need to emphasise that these are temporary measures introduced for the exceptional circumstances of the public health emergency. This does not preclude the possibility that future regulatory efficiencies could be developed as a result of this experience.

- Many countries are considering the potential of a second wave and the benefits of stockpiling. Allocation models and tools are in development across a number of agencies, including WHO, to support countries as well as global planning as needed.
- Concerns have been raised over the increased practice of compounding in pharmacies and is generally not advised.
- It is proposed to shorten future versions of the Regulatory Update and place some information on the WHO website. Previous versions could then be referenced to avoid repeating text. Details will be provided in the next update

Ethics and COVID-19: resource allocation and priority-setting

Governments, international agencies and health systems have an obligation to ensure, to the best of their ability, adequate provision of health care for all. However, this may not be possible during a pandemic, when health resources are likely to be limited. Setting priorities and rationing resources in this context means making very difficult choices, but these choices can be ethically justified. A new WHO policy brief answers a number of questions about the ethics of setting priorities for the allocation of resources during times of scarcity. Such decisions may include access to hospitals, ventilators, vaccines and medicines. It is essential that policies and practices are ethically justified in such contexts. The document provides a high-level ethical framework that can be used to guide decision-making, and complements WHO's technical guidance.

Link: Ethics and COVID-19: resource allocation and priority-setting (20 April)

In vitro diagnostics

WHO EUL for SARS-CoV-2 virus IVDs

The WHO Prequalification Unit is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2. Applicants submit their applications for assessment based on WHO instructions for NAT and antibody detection rapid tests (RDTs) submissions.

33 submissions for NAT assays have been received so far.

Link: Weekly update on the status of each application (28 April)

Four products have been listed as eligible for WHO procurement based on their compliance with WHO EUL requirements:

Date Listed	Product name	Product code(s)	Manufacturer
24 April 2020	PerkinElmer® SARS-CoV-2 Real-time RT-PCR Assay	SY580	SYM-BIO LiveScience Co., Ltd
09 April 2020	Abbott Realtime SARS-CoV-2	09N77-090 and 09N77-080	Abbott Molecular Inc.
07 April 2020	Primerdesign Ltd COVID-19 genesig Real-Time PCR assay	Z-Path-COVID-19-CE	Primerdesign Ltd.
03 April 2020	cobas SARS-CoV-2 Qualitative assay for use on the cobas 6800/8800 Systems	09175431190 and 09175440190	Roche Molecular Systems, Inc.

Link: Instruction for Use of above-mentioned products and Public Reports

Antibody detection rapid tests have been eligible for WHO emergency use assessment since 17 April.

WHO is currently working on the development of instructions for submission of antibody detection enzyme immunoassays (EIAs) and antigen detection RDTs. These will be published soon on the WHO website and the EUL eligibility expanded to such products.

COVID-19 in vitro diagnostics listed by National Regulatory Authorities in IMDRF jurisdictions

To help countries, WHO publishes links to emergency lists, together with contact details, on IVDs authorized for use in the International Medical Device Regulators Forum (IMDRF) jurisdictions along with other useful information on policies and guidance. This information is updated on a weekly basis.

Link: the most recent IMDRF update (27 April)

Note: WHO does not endorse any of the lists provided by NRAs. The information is provided exclusively to assist stakeholders with identifying the links to the various lists.

Assay comparison studies

A number of assay comparison studies are in progress. In addition to an ongoing study by FIND, which is expected to continue through May and June, the University of Colorado, USA and PATH, Seattle, USA have started studies. Both of the latter groups are using serial samples collected from cohorts of COVID-19 infected individuals.

Updated information provided by FIND is that 11 Molecular tests have completed evaluation. Evaluation protocols are now available on line.

Antigen RDT evaluations are underway and FIND will report on preliminary data when 25% enrolment has been achieved.

Links to updated information provided by FIND:

SARS-COV-2: results of molecular analyses (see new data for Certest, R-Biopharma, and Seegene)

SARS-COV-2: immunoassays

Link to evaluation protocol: Comparative evaluation of molecular tests that directly detect the nucleic acid of SARS-CoV-2

WHO advice on "immunity passports"

WHO advice on "immunity passports" was published on 24 April. This states that no study has determined that the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infection by this virus in humans.

In vitro diagnostics for detection of antibodies to SARS-CoV-2 in people, including RDTs, may identify people who have previously infected with SARS-CoV-2 but this does not indicate they have immunity to COVID-19.

Therapeutics

Clinical trials for COVID-19 treatments

Consideration to include Favipiravir in the Solidarity trial

WHO Therapeutics Working Group published a draft report of the informal consultation on the potential inclusion of Favipiravir in the solidarity trial. The objective of the call was to discuss whether newly

available evidence from 2 trials in China merit inclusion of favipiravir in the SOLIDARITY trial. The Consultation was part of the standard process for prioritization and represented an initial step towards an efficacy evaluation of favipiravir in clinical trials.

Favipiravir was approved in Japan in 2014 for the treatment of novel or re-emerging pandemic influenza virus infections. Use is limited to cases in which other influenza antiviral drugs are not sufficiently effective because favipiravir was only investigated in non-clinical studies in avian influenza A (H5N1 and H7N9), and efficacy against seasonal influenza A or B has not been sufficiently demonstrated. Favipiravir was also trialled for treating Ebola; however, there was no evidence that favipiravir monotherapy was effective.

Favipiravir has complex, nonlinear, time and dose dependent pharmacokinetics that are affected by weight. Favipiravir has anti-viral activity as a pro-drug, since favipiravir is intra-cellularly phosphoribosylated to be an active form. The Working Group considered whether it may have potential benefits early in the disease because it needs 1/ 1 ½ days to be activated and 2/ 2 ½ days to have some effect. However, lower than predicted blood levels were observed in Ebola virus disease and severe influenza patients and raise concerns about bioavailability. The WG also expressed concerns about the feasibility of high doses of favipiravir, which may require 12 or more 200 mg tablets to achieve.

There is an ongoing trial for COVID-19 in Japan with 1,800 mg twice as loading dose on Day 1 followed by 800 mg twice a day from Day 2 to 10, which seems more feasible. However results are not yet available. The US FDA recently approved 2 phase III trials in 3 hospitals for COVID-19 patients.

The WG concluded that before moving to additional phase IIb/III clinical trials or to add the favipiravir to the solidarity trial, more evidence needs to be generated.

The draft report: Informal consultation on the potential inclusion of favipiravir in the solidarity trial

SOLIDARITY trial update

Regulatory approval for the SOLIDARITY clinical trial has been obtained in 25 countries. Discussions are in progress in more than 75 other countries about starting the trial.

In response to requests for more information about the SOLIDARITY trial, adults with COVID-19 admitted to participant hospitals can join this study. Eligible patients will be asked to sign to show they understand the possible risks and benefits and consent to joining the study. The medical team responsible for each patient will check whether any of the study treatments would definitely be unsuitable.

After those checks, brief identifying details and any other conditions are digitally recorded for the patient, who is then randomly allocated to one of the study options. This may or may not involve one of the study treatments. Neither the patient nor the medical staff choose which of the study options a patient will receive, as a computer makes this allocation at random.

Critical anonymized information for the trial will only be collected at the randomization stage and when the patient is discharged or dies: which study drugs were given (and for how many days); whether ventilation or intensive care was received (and, if so, when it began), date of discharge, or date and cause of death while still in hospital.

Adults (age ≥18 years) recently hospitalised, or already in hospital, with confirmed COVID-19 and, in the view of the responsible doctor, no contra-indication to any of the study treatments will be randomly allocated between

- Local standard of care,
  OR local standard of care plus one of
- Remdesivir
- Chloroquine or Hydroxychloroquine
- Lopinavir with Ritonavir

- Lopinavir with Ritonavir plus Interferon beta-1a.

Underlying conditions recorded are: diabetes, heart disease, chronic lung disease, chronic liver disease and asthma, extending to HIV and tuberculosis in the African region. Severity of illness at entry is determined by recording: shortness of breath, being given oxygen, already on a ventilator, and, if lungs imaged, major bilateral abnormality.

Interim trial analyses are monitored by a Global Data and Safety Monitoring Committee, which is an independent group of experts.

Countries, or particular groups of hospitals, may want to collaborate in making further serial measurements or observations, relating to areas such as virology, blood gases or chemistry and lung imaging. It also possible to incorporate documentation of other aspects of disease status, for example, through linking in electronic healthcare records and routine medical databases. While well-organised additional research studies of the natural history of the disease or of the effects of the trial treatments could well be valuable, they are not core requirements.

WHO Therapeutics Working Group Terms of Reference

The ToRs for the WHO Therapeutic Working Group have been published. The criteria used by WHO to prioritize candidate therapeutics for inclusion in clinical trials are included in the document.

Link: WHO Working Group – Solidarity core protocol for therapeutics (26 April)

Research mapping of candidate therapeutics for COVID-19

A living research mapping of candidate COVID-19 therapeutics is regularly published by WHO.

Link: COVID-19 Living map of ongoing research

Living synthesis of Covid-19 study results

A group of researchers are performing a **living mapping of ongoing research** to monitor in real-time any new evidence that becomes available for treating and preventing Covid-19. In this way, gaps and deficiencies of existing evidence can be identified early enough and with an aim to help prioritizing and optimizing future research.

Through the process of **living systematic reviews** the group continuously collects and critically appraises all the available evidence addressing specific clinical outcomes related to Covid-19. Then, using **network meta-analysis** the available study results are synthesized to compare simultaneously all possible interventions that could be used in the same clinical setting. A strict process is used to identify, appraise and synthesize study results.

The group are searching and extracting data of RCTs registered in the ICTRP once a week (the WHO updates its registry every Wednesday. They are **mapping research** with the help of a team of the LIRIS/CNRS laboratory that is performing a Data Visualization.

In addition, the group are **screening electronic databases** (PubMed/Chinarxiv and MedRxiv) every day to identify results of randomized controlled trials (RCTs) and non-randomized-studies and case series. They are **collecting data** of all RCTs identified. Their main characteristics, including a complete description of the assessment of each risk of bias domain with supports for judgement and forest plots.

Evidence synthesis is performed twice a week. **Summary of findings** (SoF) tables are currently being designed.

Link: Living mapping and living systematic review of COVID-19 studies

Link: Living synthesis of study results

Classification of candidate COVID treatment types

On 28 April, WHO published a listing of candidate COVID treatment types.

Link: Classification of treatment types (28 April)

Traditional medicines

There are several ongoing clinical trials that include both western and traditional medicines. Trials for traditional medicines are being conducted according to national protocols.

WHO Guidance on trials for traditional medicines has not yet been updated for COVID 19. Traditional medicines were initially proposed to the Solidarity Trial, but the potential was not as strong as for other medicines. There are no current plans to include traditional medicines in the Solidarity Trials.

WHO will continue to provide updated information as soon as clinical findings are available.

ADR reporting and mitigation measures for drugs used for COVID 19 Management

COVID19 Solidarity Trials: Pharmacovigilance update

Vigibase, the WHO global database of Individual Case Safety Reports (ICSR) continues to see a steady rise in the number of case safety reports related to drugs that are used in the treatment of Covid-19. There are now 456 reports from 4 WHO regions, with the majority of the reports coming from the European region (87.7%). More reports involve men (68%) than women (29%), while 66% of the reports are classified as "serious". Most of the reports include at least one of the drugs that are being investigated in the SOLIDARITY trial, with the drug described either as "suspected" to have caused the event or ''interacting" with other drugs. A small number of additional reports describing other drugs that are being used in the treatment of COVID-19 disease.

The most commonly reported ADRs continue to be those included in available product labelling. Overall, QT prolongation and hepatic events are the most commonly reported serious events. Renal events and skin events, including one case of toxic epidermal necrolysis, have also been reported.

Link: Descriptive analysis of COVID19-related spontaneous related spontaneous reports from VigiBase (19 April)

Vaccines

SOLIDARITY clinical trial protocol for candidate SARS-CoV-2 vaccines

This large, international, randomized controlled clinical trial is designed to enable an expeditious, agile and concurrent evaluation of the benefits and risks of multiple candidate preventive vaccines against COVID-19 at international sites with sufficient COVID-19 attack rates. Different candidate vaccines may be available or suitable to enter the trial at different times; for each candidate vaccine, the primary efficacy results are expected within 3-6 months of the vaccine entering the trial.

On 30 April, WHO launched a call for interest in engagement of vaccine trial sites in evaluation of COVID19

vaccines in adaptive multi-country global Solidarity Vaccine Trial.

Link to the call: Interest in engagement of vaccine trial sites (30 April)

Regulators are invited to review the draft protocol, preferably in regional groupings, and provide comments as soon as possible.

Link to the draft protocol: An international randomised trial of candidate vaccines against COVID-19 (19 April)

Draft criteria for prioritization by WHO of vaccines for SARS-CoV-2

Proposed attributes and minimal acceptability criteria have been published to provide considerations for the assessment and prioritization of COVID-19 candidate vaccines by WHO. The attributes and minimal acceptability criteria will be relevant in WHO's case-by-case assessments of COVID-19 vaccines in the future. Should a vaccine's profile be sufficiently superior to the critical characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Vaccines which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO's processes.

Link: Criteria for COVID-19 vaccine prioritization (28 April)

Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO. There are 8 vaccines in clinical trial and 94 in pre-clinical development. The non-replicating ChAdOx1 vector phase 1/2 trial, which started in the UK on 23 April, has the largest number target sample size, of 1112, with an update expected in September 2020. A 500-person phase 2 trial started in China on 20 April of the non-replicating adeno 5 vector.

Link: Draft landscape of COVID 19 candidate vaccines (30 April)

WHO/SEARO convenes manufacturers and regulatory authorities to meet on COVID-19 vaccines

Gearing up for the much needed COVID-19 vaccines, the SEARO organized a meeting on 28 April of vaccine manufacturers and national regulatory authorities from its South-East Asia Region.

India, Indonesia and Thailand are among the world's largest vaccine manufacturers. Every day, millions of people of all ages are provided life-saving protection by vaccines produced in these three countries. The manufacturing capacity that exists in the Region is of the quality and scale required to produce and roll-out a COVID-19 vaccine globally. At the virtual meeting, leading manufacturers from India, Indonesia and Thailand discussed timelines and production capacity, while regulatory bodies deliberated on adjustments that would be needed in processes to make COVID-19 vaccines available at the earliest.

Enabling research; animal models, clinical trial protocols, assay development, standards

WHO Working Group on Assays and Reference Preparations

The 29 April meeting of the Working Group was extended, for the first time, to vaccine developers. It is intended to include vaccine developers in future calls at monthly intervals.

The WG Chair, Bill Dowling (seconded to WHO by CEPI) started the meeting by providing a synthesis of the discussions of the WG over the last 8 weeks. The group had discussed (a) sources of SARS-CoV-2 viruses for

use as reagents in assays; (b) protein reagents; (c) antibody reagents; (d) ELISA assays (e) neutralization assays (f) cross-reactivity between SARS-CoV-2, SARS-CoV-1, MERS-CoV, and the four other human coronaviruses, (g) assay comparison studies, (h) and interactions with other WHO WGs, notably the groups providing advice on serosurveys ("SOLIDARITY 2" studies), on laboratory diagnosis, and on animal models.

Questions from vaccine developers identified a need for the WG to obtain information on assays for mucosal immunity to SARS-CoV-2. There is also a need to clarify that the synthesis of information provided to the WG represents a summary of state-of-the art scientific thinking but does not necessarily represent WHO normative guidance.

WHO Working Group on Animal Models

The 30 April meeting of the Working Group was extended, for the first time, to vaccine developers. It is intended to include vaccine developers in future calls at monthly intervals. In the meeting 19 vaccine developers briefly outlined their work, with an emphasis on animal models that are being used to support product development. A general issue that vaccine developers have not yet solved is how to test for the possibility of vaccine enhanced disease. The WG advised that, as yet, a model is not established. PHE, UK, are attempting to develop a positive control that will induce vaccine enhanced disease, with plans that it would be made available to producers. Experiments with animal models of vaccine enhanced disease caused by RSV vaccines have found that a range of vaccine dilutions need to be tested to identify suitable doses to induce this phenomenon.

The meeting started with an overview of progress made by the group. The main findings so far are that SARS-CoV-2 causes mild disease in animal models, but with virus shedding in nasal and rectal swabs, and moderate lung pathology. In-bred laboratory strains of mice are not susceptible to SARS-CoV-2 infection, but transgenic mice expressing the human ACE-2 receptor are. Hamsters show moderate disease on infection with SARS-CoV-2 and golden Syrian hamsters are being widely used in studies. Ferrets are also being widely used, but show only mild disease symptoms. Rhesus macaques in one laboratory have been shown to have moderate clinical symptoms on infection, but other laboratories report only mild symptoms. The reasons for this discrepancy are not yet clear. One reinfection study has been reported in rhesus macaques in which animals that had recovered from an initial SARS-CoV-2 challenge were resistant to reinfection with the same strain. Cynomolgus macaques have been found to have milder diseases than rhesus macaques.

Falsified and substandard products

The UN secretary general has tasked the UNODC to write a high-level report on organized crime in relation to Covid19. This report will be written in coordination/collaboration with the WHO, as a sister agency.

It is anticipated that one of the key recommendations will be to ensure that the national law enforcement authorities coordinate/collaborate closely with the national health/medicine regulatory authorities.

Supply chain

Issues noted from WHO Regional Offices

Several member states have requested support in identifying an appropriate list of medicines in ICU settings. A general list of medicines to support treatment of COVID patients is available.

Control click to download the Quantification tool WHO COVID-19 Essential Supplies Forecasting Tool

A list specific to managing COVID patients in ICU settings (e.g., medicines and specific formulations for intubated patients) has been developed by PAHO.

Link: Essential Medicines List for Management of Patients admitted to Intensive Care Units with Suspected or Confirmed COVID-19 Diagnosis (09 April)

Concerns have been raised over the increased practice of compounding in pharmacies and is generally not advised.

Shortages

Shortages of specific products continue. There are a number of factors impacting medicine supply in countries of all income levels. WHO is working with industry associations and regulators for solutions wherever possible.

The main factors, which compound on each other, include the following:

- A continual shift in demand for certain medicines, where some medicines are now increasing in demand due to the reinstatement in some countries of access to services for non-urgent conditions.
- Increased freight costs, with an informal industry survey showing an average increase globally of approximately 225%; however, there is a disproportionate impact on low- and middle-income countries, with specific lanes showing increases of more than 400% and one over 1000%.
- Speculative procurement of medicines in clinical trials.
- Continued high demand for certain ICU medicines, which while has stabilized in some countries, is increasing in others;
- Intra-country competition for medicines between hospitals and facilities providing palliative care, especially for
- Medicines using the same primary ingredients as those moving into high demand;
- Export restrictions, which continue to emerge and abate;
- Continued production slowdowns related to quarantine measures and inability to obtain materials;
- Continued limitations on transportation and warehousing services, including inter-country and intra-country transport.

A partial list of medicines reported to be in shortage include the following:

- Antibiotics: azithromycin, levofloxacin, metronidazole, amoxiclav
- Antipsychotics: haloperidol
- Benzodiazepine sedatives: midazolam and lorazepam
- Diagnostic test kits
- Epinephrine and norepinephrine
- HIV: Lopinavir/ritonavir
- Malaria treatments (hydroxychloroquine, chloroquine, Artemether-lumafantrine, Artemisinin-based combination therapies, Sulfadoxine-pyrimethamine + amodiaquine).
- Muscle relaxants
- Neuromuscular relaxants: succinylcholine, atracurium, or vecuronium.
- Nonbenzodiazepine sedatives: propofol
- Opioids: morphine and fentanyl
- paracetamol
- PPE
- Renal replacement fluids

Other medicines remain under a watch status to monitor their availability, including primary health care medicines and other ICU medicines.

Regulators and procurers are working together to find solutions to these problems on a country by country basis, including:

- alternative supply sources and the regulatory flexibilities to facilitate the implementation;
- global labeling to facilitate broader releases to markets
- shifting patients to alternative therapies (in the case of lopinavir/ritonavir)
- allocation models that allow for optimized distribution of medicines within a given country
- allocation models for eventual new medicines, pending outcomes of clinical trials

WHO continues to monitor shortages across regional networks, industry associations and regulatory networks.

Many countries are considering the potential of a second wave and the benefits of stockpiling. Allocation models and tools are in development across a number of agencies, including WHO, to support countries as well as global planning as needed.

Consolidation of UN procurement

WHO coordinates a group of UN partners, including multiple subgroups that are distributing PPE and other supplies. Major shipments of PPEs have been made, and more are scheduled in weeks to come. Over 100 shipments of PPEs and equipment have been made and another 23 are scheduled in the coming days.

The World Food Programme, which is a member of the UN collaboration, has recruited aviation assets for many routes and continues to identify transportation options for countries that are particularly vulnerable to the transportation and market slowdowns. Shortages and insufficient manufacturing capacity are impacting the supply of products, including oxygen equipment, some PPEs and others.

Communications information about the UN consolidation efforts are under development to regularly share information.

Transportation

Transportation remains a critical problem and is linked to increasing shortages in some countries. The problem of limited flight availability as well as intra-country transportation have been cited by multiple countries.

Two countries have started collaborations with major carries to repurpose some passenger flights to carry cargo, but more action will be needed to assure that flights, warehouse staff and transportation staff are able to safely return to work in affected countries and sub-national regions.

See the note on deliveries by the World Food Programme above.

Manufacturing capacity

While manufacturing capacity in China is reported to have normalized, not all companies have recovered completely. The confinement measures in India continue to impact access to factories, warehouses and transportation services. Continued diplomatic discussions are underway to identify means to safely increase manufacturing production, including the availability of solvents, intermediates and packaging components.

The progress towards increased production from India, however, remains more limited than anticipated. The WHO Country Office in India remains engaged with in supporting various high-level working groups across Ministries within the Government of India to identify solutions.

Export restrictions

Export restrictions continue to exacerbate the already chaotic landscape of access to medicines. While some restrictions were recently lifted, two countries recently implemented new export restrictions. In spite of multiple calls to action from WHO, WTO and other UN partners, these restrictions continue to emerge.

Link: Joint statement by WTO and WHO (20 April)

Procurement of medicines for clinical trials

For countries wishing to access medicines for use in the Solidarity Trials, requests can be made through the Solidarity Trial team. It should be noted that confirmation that medicines are part of sanctioned trials (e.g., approved by an Ethics Review Board, the National Medicines Regulatory Authority and any importation permits) must be available in advance of requesting the medicines.

For the limited number of medicines that are in trials, but that also have existing indications (e.g., hydroxychloroquine and lopinavir-ritonavir), procurement support remains available from UN partners for normal programmatic use outside of clinical trials (i.e., for treatment of malaria, HIV).

Medical Devices

List of priority medical devices for COVID-19 case management

This list presents the different types of medical devices including medical equipment, personal protective equipment (PPE), and other medical supplies for the management of COVID-19 patients. The list describes alternative options that should be considered based on available infrastructure, health workforce and technologies. These devices are listed in no priority order. Please note some are capital equipment that requires accessories, spare part and extended warranties, for more information please consult the technical specifications listed below and the manufacturer's recommendations.

Link: Control click to download List of priority medical devices

Technical specifications for invasive and non-invasive ventilators for COVID-19

These technical specifications describe the minimum requirements that invasive and non-invasive ventilators must comply with to ensure quality, safety and effectiveness when used for the management of COVID-19. All these ventilators should be provided with accessories, consumables and spare parts as required to operate for minimum duration of 3 months. It is advisable to follow the maintenance guidance for the replacement of accessories and consumables, and for the safe decontamination of the reusable parts provided by the manufacturer.

Link: Technical specifications for invasive and non-invasive ventilators (15 April)

Oxygen sources and distribution for COVID-19 treatment centres

This interim guidance on oxygen sources and distribution strategies for COVID-19 treatment has been adapted from WHO and UNICEF's technical specifications and guidance for oxygen therapy devices, which is part of the WHO medical device technical series. This guidance is intended for health facility administrators, clinical decision-makers, procurement officers, planning officers, biomedical engineers, infrastructure engineers and policy-makers. It describes how to quantify oxygen demand, identify oxygen sources that are available, and select appropriate surge sources to best respond to COVID-19 patients' needs, especially in low-and-middle income countries.

Link: Oxygen sources and distribution for COVID-19 treatment centres (09 April)

Non-medical masks

Some countries have asked for guidance on non-medical masks. These are not medical devices and therefore out of the scope of the medical device regulatory oversight authorities. As an example, see the link to a US FDA statement.

Link: Enforcement Policy for Face Masks and Respirators During the Coronavirus Disease (COVID-19) Public Health Emergency (Revised) (April 2020)

Sharing information with regional regulatory groups

Regional Regulatory Group Meetings

WHO HQ joined meetings with regulators in the EMRO and EURO regions, each of which had been arranged by the respective WHO Regional Office. The meetings aimed to better identify ways in which WHO could support regulators and ways in which regulators could help one another. Each meeting was attended by more than 50 participants.

The difficulties of conducting GMP inspections under conditions of travel and social distancing restrictions was raised in discussion. Regulatory flexibility and regulatory reliance are seen as solutions to this problem with, as an example, reliance on inspections conducted by other authorities. Innovations such as use of video tools to conduct virtual inspections of critical manufacturing processes is also being explored.

Regulatory reliance will be particularly important for assessment of candidate vaccines against SARS-CoV-2 as many candidates use novel and complex vaccine platforms. Joint reviews of clinical trial applications are particularly encouraged.

Many countries had questions on regulation of PPEs and IVDs, and continued guidance from WHO will be much appreciated. Serological tests for IVDs was a hot topic and regulators were urged to continue to stress that such tests play an important role in research and surveillance but are not currently recommended for case detection.

NRAs were encouraged to report adverse events associated with treatments for COVID-19 and also to ensure prompt reporting of substandard and falsified products.

Regulatory Flexibility initiatives

In order to mitigate the risks of shortages and stockouts, a number of regulators have produced temporary guidance on regulatory flexibility. Some examples are included below. The table includes new entries from Indonesia, Singapore and Switzerland. WHO is working with international regulators to develop best practices.

One concern expressed by regulators is that product developers may expect regulatory flexibilities introduced in the context of the COVID-19 public health emergency to be carried forward once the emergency is over. Communications on regulatory flexibilities needs to emphasise that these are temporary measures introduced for the exceptional circumstances of the public health emergency. However, it would be reasonable for regulators to review lessons learned from application of the flexibilities to determine if future regulatory efficiencies could be developed as a result of this experience.

EU	Regulatory flexibility guidance	ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf
US FDA	Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency	www.fda.gov/media/136238/download
US FDA	Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic	www.fda.gov/media/72498/download
US FDA	Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act	www.fda.gov/media/136486/download
UK MHRA	Exceptional good distribution practice (GDP) flexibilities for medicines during the coronavirus (COVID-19) outbreak	www.gov.uk/guidance/exceptional-good-distribution-practice-gdp-flexibilities-for-medicines-during-the-coronavirus-covid-19-outbreak
UK MHRA	Exceptional GMP flexibilities for medicines imported from third countries during the coronavirus (COVID-19) outbreak	www.gov.uk/guidance/exceptional-gmp-flexibilities-for-medicines-imported-from-third-countries-during-the-coronavirus-covid-19-outbreak
UK MHRA	MHRA regulatory flexibilities resulting from coronavirus (COVID-19) – covering: Blood components for transfusion; Clinical trials; Inspections and good practice; Medical Devices; Medicines regulation; Pharmacovigilance.	www.gov.uk/guidance/mhra-regulatory-flexibilities-resulting-from-coronavirus-covid-19
CA HC	Exceptional Access to Drugs	www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/information-provisions-related-drugs-biocides.html
CA HC	Diagnostic Devices	www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/covid-19.html
CA HC	Hard Surface Disinfectants and Hand Sanitizers	www.canada.ca/en/health-canada/services/drugs-health-products/disinfectants/covid-19.html
CA HC	Exceptional Access to Medical Devices	www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/medical-device-exceptional-import.html
AU TGA	TGA response to coronavirus (COVID-19) – covering: Medicine shortages; Access to coronavirus tests, medicines and vaccines; Advertising of products; GMP information for sponsors and manufacturers;	www.tga.gov.au/media-release/tga-response-coronavirus-covid-19
AU TGA	Post market review of COVID-19 point-of-care tests	www.tga.gov.au/post-market-review-covid-19-point-care-tests
AU TGA	Exemption for coronavirus (COVID-19) medical devices	www.tga.gov.au/exemption-coronavirus-covid-19-medical-devices

AU TGA	COVID-19 limits on dispensing and sales at pharmacies	www.tga.gov.au/media-release/covid-19-limits-dispensing-and-sales-pharmacies
AU TGA	Expedited COVID-19 medical device application process	www.tga.gov.au/expedited-covid-19-medical-device-application-process
JP PMDA	Handling on regulatory reviews of drugs, medical devices, IVDs, and regenerative medical products for the time being associated with COVID-19 (Administrative Notice dated April 13, 2020) → The notice writes that medical products related to COVID-19 are subject to priority review.	www.mhlw.go.jp/hourei/doc/tsuchi/T200415I0010.pdf
JP PMDA	Handling on clinical trial notifications of COVID-19 (Administrative Notice dated March 19, 2020) → The notice permits that clinical trials on COVID-19 can be started without waiting 30 days after the submission of clinical trial notification if investigation by PMDA is completed	www.mhlw.go.jp/hourei/doc/tsuchi/T200323I0040.pdf
JP PMDA	Handling on the storage of informed consent forms during clinical trials (Administrative Notice dated April 7, 2020) → The notice permits that alternative method can be used when signed informed consent forms are difficult to be stored because of infection etc. in clinical trials for patients with infectious disease.	www.mhlw.go.jp/hourei/doc/tsuchi/T200408I0010.pdf
JP PMDA	Handling on adverse drug reaction reports of medical products in dealing with COVID-19 (Administrative Notice dated March 9, 2020) → The notice permits that adverse drug reaction reports can be simplified (including omission of seal) during COVID-19 pandemic.	www.pmda.go.jp/files/000234755.pdf
JP PMDA	Q&A on clinical trial of drugs, medical devices, and regenerative medical products under the influence of COVID-19 → The notice permits flexibility in handling investigational products and having IRB	www.pmda.go.jp/files/000234815.pdf
SP EMPS	Guidance on exceptional measures on clinical trials and observational studies to handle problems arising from COVID-19 emergency. - Dedicated webpage with the repository of guidance and updates regarding COVID19	www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/
IN CDSCO	Circular regarding procedure for lot release of Human vaccine in view of prevailing COVID-19 pandemic	https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTgxNg
ID BADAN POM	Establishment of Drug Guidelines in the Handling of Corona Virus Disease 2019 (COVID-19)	https://jdih.pom.go.id/produk/KEPUTUSAN%20KEPALA%20BPOM/Kep%20KBPOM%20tentang%20Pedoman%20Obat%20dalam%20Penanganan%20COVID%2019_Lengkap.pdf
SG HSA	HSA Expedites Approval of COVID-19 Diagnostic Tests in Singapore via Provisional Authorisation	www.hsa.gov.sg/announcements/regulatory-updates/hsa-expedites-approval-of-covid-19-diagnostic-tests-in-singapore-via-provisional-authorisation
SG HSA	Import of Hand Sanitisers, Masks, Thermometers and Protective Gear	www.hsa.gov.sg/announcements/regulatory-updates/import-of-hand-sanitisers-masks-thermometers-and-protective-gear

SG HSA	HSA's Regulatory Position on Respiratory Devices: Supply for Management of COVID-19 Patients	www.hsa.gov.sg/announcements/regulatory-updates/hsa-regulatory-position-on-respiratory-devices-supply-for-management-of-covid-19-patients
SG HSA	Advisory on products claiming to prevent or treat COVID-19 (Coronavirus Disease 2019)	www.hsa.gov.sg/consumer-safety/articles//details/advisory-on-products-claiming-to-prevent-or-treat-covid-19-(coronavirus-disease-2019)
CH swissmedic	Clinical trials on medicinal products - Pandemic by SARS-CoV-2	www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/klv-cov-2-pandemie-2.html
CH swissmedic	Inspections in Switzerland during the COVID-19 pandemic	www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/durchfuehrung-inspektionen-waehrend-covid.html
CH swissmedic	Pharmacovigilance: change in procedure for requesting follow-up information for individual case safety reports	www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/pharmakovigilan_geaendertes_vorgehen_follow-up_info.html
CH swissmedic	COVID-19: Exceptions from import provisions for medicinal products	www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/covid-19-ausnahmen-einfuhrbestimmungen-am.html
CH swissmedic	Placing on the market of important medical devices for combating the COVID-19 pandemic	www.swissmedic.ch/swissmedic/en/home/medical-devices/market-surveillance-of-medical-devices/announcements-on-market-control-issues/inverkehrbringung_lebenswichtiger_beatmungsgeraete.html

Access to regulatory updates by WHO staff

All WHO staff have access to the Regulatory Updates at the following location:

P:\PubPersons\RPQ\COVID_Regulatory_Updates