Regulation of *in vitro* diagnostics, therapeutics, and vaccines
WHO Update – 5
Coronavirus disease 2019 (COVID-19)
17 Apr 2020

World Health Organization

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Key Messages

In order to mitigate the risks of shortages and stockouts, a number of regulators have produced temporary guidance on regulatory flexibility. WHO will work with international regulators to develop best practices.

To support Member States to access validated rapid diagnostic tests which detect antibodies as a tool for epidemiological studies, the scope of the WHO EUL procedure has been expanded to help identify appropriate assays. The scope will be further expanded to include rapid diagnostic tests for antigen in the near future.

Highlights and main issues

- WHO published an update to its COVID-19 strategy on 13th April
- Four countries, Norway, Spain, Iran and Switzerland, have already launched SOLIDARITY clinical trials for COVID-19 treatments.
- The first descriptive analysis of COVID19 treatment-related spontaneous adverse event reports from VigiBase has been prepared.
- A synopsis of a phase IIb/III SOLIDARITY clinical trial protocol for candidate SARS-CoV-2 vaccines has been posted by WHO.
- WHO Target Product Profiles for SARS-CoV-2 Vaccines have also been posted.
- The current environment of speculative purchasing and shortages of certain medicines is having a disproportionate impact on LMICs.
- A number of regulators have announced specific regulatory flexibility guidance

COVID 19 Strategy Update

This strategic preparedness and response plan outlines the public health measures that the international community stands ready to provide to support all countries to prepare for and respond to COVID-19. The update takes what we have learned so far about the virus in the 100 days since the public health emergency of international concern was declared and translates that

knowledge into strategic action that can guide the efforts of all national and international partners when developing context-specific national and regional operational plans.

www.who.int/publications-detail/covid-19-strategy-update-13-april-2020

In vitro diagnostics

WHO EUL for SARS-CoV-2 virus IVDs

The WHO Prequalification Team is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2. So far, only assays for the detection of SARS-CoV-2 nucleic acid were eligible for EUL assessment.

As 17 April 2020 WHO had listed three products under the Emergency Use Listing procedure for in vitro diagnostics as eligible for procurement.
The list is at: :www.who.int/diagnostics_laboratory/200409_eul_sars_cov2_product_list.pdf?ua=1

A further 23 submissions to WHO are being assessed. At least another 6 submissions are expected.

Information on applications received, which is updated weekly, can be found at:
www.who.int/diagnostics_laboratory/200414_eul_covid19_ivd_update.pdf?ua=1

Scope of the WHO EUL expanded to RDTs for antibodies

Several Member States have expressed high interest in access to rapid tests which detect antibodies or antigen as a tool for epidemiological studies. The WHO interim guidance *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* (see Regulatory Update 4) recommends that such tests must be validated in the appropriate populations and settings. WHO therefore decided that the scope of the EUL procedure will be expanded to help identify point-of-care assays which will support Member States is such efforts.

On 17 April 2020 WHO launched a call for expression of interest for rapid antibody detection tests, www.who.int/diagnostics_laboratory/EUL/en/.

The call for EOI includes a link to WHO technical specifications which guide manufacturers in their submissions and will be used by WHO for assessing the technical documentation submitted by applicants. Antigen detection rapid tests will be added to the EUL scope in the near future.

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. **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.**

The most recent update was published on 14 April. The links can be found at:
www.who.int/diagnostics_laboratory/200414_imdrf_collated_table_14_april_2020.pdf?ua=1

EU guidelines on IVDs

The European Commission has published Guidelines on COVID-19 IVDs and their performance. It outlines the regulatory context of COVID-19-related in vitro diagnostic testing devices in the EU and gives an overview of different types of tests and their purposes. It includes considerations on device performance and validating that performance.

The document is available at: COMMUNICATION FROM THE COMMISSION Guidelines on COVID-19 in vitro diagnostic tests and their performance

WHO Working Group on Assays and Reference Preparations

In the most recent meeting of the group, FIND reported preliminary findings from an independent evaluation of molecular tests. Products were selected for evaluation from over 200 submissions received in response to an expression of interest (EOI). The evaluations are going more slowly than expected due to problems with supply of tests for the evaluation. For molecular tests, FIND have ordered 55 tests, 19 have been delivered and 5 have completed evaluations (see below). The delivery problems are of two types:

- orders from FIND (which are small quantity) being given lower priority than large orders for other customers
- tests from China need regulatory approval for export.

The results of the 5 evaluations of molecular tests have been completed and posted by FIND. All tests had 100% clinical sensitivity and between 96-100% clinical specificity.

For further information see: www.finddx.org/covid-19/

Therapeutics

SOLIDARITY clinical trials for COVID-19 treatments and new developments

In order to fast-track research on existing anti-viral drugs be effectively repurposed to target COVID-19, WHO launched "Solidarity" on March 18 as a large international clinical trial to help find an effective treatment for COVID-19. Enrolling patients in one single randomized trial will help facilitate the rapid worldwide comparison of unproven treatments and overcome the risk of multiple small trials not generating the strong evidence needed to determine the relative effectiveness of potential treatments.

To begin with, Solidarity trial is to compare against the standard of care, four treatment options based on evidence from laboratory, animal and clinical studies: Remdesivir; Lopinavir/ Ritonavir; Lopinavir/Ritonavir with Interferon beta-1a; and Chloroquine or Hydroxychloroquine. By enrolling patients in multiple countries, the Solidarity trial aims to rapidly discover whether any of the drugs slow disease progression or improve survival.

In support of the Solidarity trial, WHO negotiated agreements with 5 manufacturers of the trial drugs that will donate these to participating countries.

Since its launch, **95 countries** have expressed an interest in participating in the Solidarity trial and approached WHO for support. Of these, four countries have launched trials: **Norway, Spain, Iran and Switzerland**. Another six countries are expected to launch Solidarity this week and another 10 are anticipated to launch next week.

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

Landscape of candidate therapeutics for COVID-19

A landscape analysis of candidate COVID-19 therapeutics is regularly published by WHO.

The analysis is available at:
https://app.powerbi.com/view?r=eyJrIjoiNjQxZWZhOTItYzU1ZS00Y2QxLWE1ODAtOTViZjhmNjEyZjNiIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9

Web-based application to analyse clinical trials to evaluate therapeutics for COVID-19

The application is available at:
https://app.powerbi.com/view?r=eyJrIjoiMjA1ZDA0N2YtOTUzMi00ZTU1LWFlMDAtMjFlMTVkN2U2ODQyIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9

ICMRA virtual meeting on real world evidence observational studies

In a dedicated COVID-19 workshop convened on 6 April under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA), regulators discussed how data generated during clinical practice could complement evidence from clinical trials with potential therapeutics or vaccines against COVID-19. Participants from more than 25 countries, representing 28 medicines regulatory authorities globally and experts from WHO and the European Commission acknowledged the importance of observational studies of real world data for increasing the effectiveness and efficiency of regulatory processes and decision-making in the development, authorisation and monitoring of medicines and vaccines to prevent and treat COVID-19 and to address knowledge gaps that cannot be addressed by clinical trials.

The report of the meeting is available at: www.icmra.info/drupal/sites/default/files/2020-04/Summary%20of%20ICMRA%20meeting_Observational%20studies%20and%20RWE.pdf

Increase in ADR reporting for drugs used for COVID 19 Management

During the month of March 2020, 26 reports in relation to treatment for COVID 19 with drugs included in the WHO SOLIDARITY trial were retrieved from Vigibase, the Global individual case safety reports database.

Details are presented in the attached Annex. Regular updates, and links to their posting, will follow.

Vaccines

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

The goal of the protocol is to coordinate evaluation of the many preventive candidate SARS-CoV-2 vaccines under development, to evaluate promptly, efficiently and reliably their safety and efficacy, enabling assessment of whether any are appropriate for deployment to influence the course of the pandemic. A large international multi-site individually randomized controlled clinical trial will enable the concurrent evaluation of the benefits and risks of each promising candidate vaccine within 3-6 months of it being made available for the trial. The adaptive trial design enables candidate vaccines to be added to the trial as they become available if they meet prioritization criteria (to be defined via the WHO vaccine prioritization group). As compared with conducting separate trials for each candidate vaccine, the trial design, which evaluates candidate vaccines in parallel with a common placebo group increases the likelihood that participants receive one of the candidate vaccines while improving the efficiency of the clinical trial, promoting efficient allocation of world-wide clinical trial resources, and increasing the likelihood that effective vaccines will be quickly, efficiently and reliably evaluated.

All sites with sufficient transmission rates at the time of entering the trial can participate. Participating sites must be able to determine whether trial participants develop COVID-19, perform safety follow-up, and assure multiple ways to contact participants to assure follow-up and retention. Adults in locations considered at high risk for exposure to SARS-CoV-2 will be enrolled. After supportive safety data are available for a given vaccine, enrolment in some sites will be extended to include immunocompromised, pregnant, or lactating individuals.

The document is at:
www.who.int/blueprint/priority-diseases/key-action/Outline_CoreProtocol_vaccine_trial_09042020.pdf?ua=1

WHO Target Product Profiles for COVID-19 Vaccines

This document describes the preferred and minimally acceptable profiles for human vaccines for (a) long term protection of persons at high ongoing risk of COVID-19 such as healthcare workers and (b) reactive use in outbreak settings where rapid onset of immunity is required. The target audience includes vaccine scientists, product developers, manufacturers and funding agencies.

Criteria are described that lay out some of the considerations that will be relevant in WHO's case-by-case assessments of COVID-19 vaccines in the future. Therefore, 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.

All the requirements contained in WHO guidelines relevant to WHO policy recommendation and prequalification will also apply.

The document is at: www.who.int/blueprint/priority-diseases/key-action/WHO_Target_Product_Profiles_for_COVID-19_web.pdf?ua=1

WHO welcomes your contributions and/or feedback to the document. Please send an email to lauriex@who.int no later than 24 April 2020.

Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO.

The 11 April 2020 version is available at: www.who.int/blueprint/priority-diseases/key-action/Novel_Coronavirus_Landscape_nCoV_11April2020.PDF?ua=1

Blood supply and use of blood components in the response to COVID-19

Convalescent plasma trials

The current situation where vaccines or potential drugs for COVID-19 is not yet available has prompted several countries to use convalescent plasma (CP) for treatment either in clinical trials or in compassionate use. WHO is committed to liaise with its international partners to obtain and share information on countries conducting studies on CP. Position statements and/or study protocols for evaluation of CP have been issued by a number of Member States and are listed in the table. **WHO does not endorse any of the statements or protocols. The information is provided exclusively to assist stakeholders with identifying the links to the various statements and protocols.**

INITIATOR	TITLE OF DOCUMENT	LINK TO THE DOCUMENT
Saudi Arabia, King Abdulaziz University Jeddah	Use of Convalescence Plasma in The Treatment of Patients Infected with Covid-19 Virus Infection Protocol Version V 1.2	isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/
SIMTI (Societa Italiana di Medicina Transfusionale e Imunoematologia) SIdEM (Societa Italiana di Emaferesi e Manipulazione Cellulare)	Convalescent Plasma “Position paper” on the preparation of immune plasma to be used in the treatment of patients with COVID-19	isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/
US FDA	• National initiative to provide COVID-19 Convalescent Plasma for use in controlled trials • Expanded access to Convalescent Plasma for the Treatment of Patients with COVID-19 • National COVID-19 Convalescent Plasma Project	• www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19. • www.uscovidplasma.org. • https://ccpp19.org/
UP-Philippine General Hospital Technical Working Group on Convalescent Plasma Therapy	Guide on The Compassionate Use of Convalescent Plasma Therapy for Covid-19	isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/
European Commission Directorate-General for Health and Food Safety Directorate B - Health systems, medical products and innovation	An EU programme of COVID-19 convalescent plasma collection and transfusion Guidance on collection, testing, processing, storage, distribution and monitored use	ec.europa.eu/health/blood_tissues_organs/covid-19_en
ISBT Working Party on Global Blood Safety	Points to consider in the preparation and transfusion of COVID-19 convalescent plasma	isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources/

INITIATOR	TITLE OF DOCUMENT	LINK TO THE DOCUMENT
U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research	Investigational COVID-19 Convalescent Plasma Guidance for Industry	isbtweb.org/coronaoutbreak/convalescent-plasma-covid-19-resources
African Blood Regulator Forum (ABRF)	African Blood Regulator Forum (ABRF) Position on Convalescent Plasma Use in Africa as potential therapy to COVID-19	Under development

Discussions are ongoing with the WHO R&D Blueprint Working Group on Therapeutics, in response to requests from Regional Advisors, Member States and ECBS Blood Tract Members, to provide a WHO position statement and template protocol for CP for COVID-19 treatment.

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

WHO Working Group on Animal Models

The Working Group was requested by the Secretariat to develop a global collaborative screening process, based on a standard protocol for testing in animals, to assess all candidate vaccines identified by WHO. The intent is to prioritize the more than 100 candidates identified so far to go forward into first-in-human clinical trials. An initial draft is available for comment. Care will be needed to ensure that the purpose of this initiative is to facilitate prioritization of candidate vaccines and to support regulatory decision making. The animal models research community will be asked to respond to a call to participate in this unprecedented global effort.

Supply chain

Issues noted from WHO Regional Offices

The current environment of speculative purchasing and shortages of certain medicines is having a disproportionate impact on LMICs. WHO and UN partners are receiving increasing requests to assist with sourcing of critical medicines, including ICU medicines, and antibiotics.

Donation initiatives

Donation programs have emerged through bi-lateral initiatives, notably an initiative from the Government of Japan who has offered to donate Favipiravir to a number of countries.
WHO reminds donation initiatives to be mindful of Good Donation Practices, which capture principles of what constitutes a useful donation versus those that can actually add additional strain to health systems.

Consolidation of UN procurement

Due to the significant fragmentation of medicines markets around the world, UN procurers are working to harmonize demand to avoid any further fragmentation. The current focus of the harmonized efforts is currently diagnostics, PPE, oxygen and ventilators. To that end, a quantification tools and training

modules have been developed and released. In addition, a costing tool for countries seeking support from the international development community has been developed to streamline request for support. While the costing tool is focused on overall health system surge capacity, it also addresses transportation, PPEs and other equipment.

WHO coordinates a group of UN partners, including multiple subgroups that are distributing PPE and other supplies. Notably, a major shipment was released to a supply hub in Addis Ababa for onward distribution to countries in the AFRO region. A consolidated tender for additional products is expected shortly and will be released by UNICEF on behalf of the UN consortium.

Procurement of medicines for off-label use

WHO and partners are receiving increasing requests to procurement medicines that include some of the repurposed medicines currently in clinical trials. While evidence is yet inconclusive regarding the use of the repurposed medicines, some countries' national medicines regulatory authorities have approved their use in treatment of COVID patients. WHO will continue to respond to requests for these medicines for use as indicated as well as for use in clinical trials. In addition, WHO will respond to requests for procurement involving off-label use provided that the requesting country demonstrates that the use has been approved by the national medicines regulatory authority.

More information at: www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19

Technical specifications:

To facilitate procurement, technical specifications have been developed for a range of products, including PPEs, oxygen and ventilators. Non-invasive ventilators are also addressed in the new specifications. There is limited capacity to test products against performance standards, and care should be used when procuring from unknown or unvalidated sources.

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, plus others:

- Panic and speculative procurement of medicines in clinical trials;
- Increased freight costs, in some cases reaching 1000%;
- Spikes in demand for specific medicines, especially for certain ICU medicines;
- Medicines using the same primary ingredients as those moving into high demand;
- Export restrictions, which are starting to ease in some areas;
- Production slowdowns related to quarantine measures and inability to obtain materials;
- Limited transportation, including inter-country and intra-country transport, affecting exports of medicines.

In some countries, authorities are monitoring national supply chain and consumption to redistribute medicines to avoid facility level stock outs. This is occurring across markets of all income levels. In addition, guidance on the use of medicines to reduce any over-prescribing or hording has been developed.

A partial list of medicines reported to be in shortage include the following:
Albuterol inhalers, Artemether-lumafantrine, Artemisinin-based combination therapies, Azithromycin, Chloroquine and Hydroxychloroquine, Epinephrine and Norepinephrine, Fentanyl, Injectable artesunate, Lopinavir/ritonavir, Muscle relaxants, Paracetamol, Propofol, Sulfadoxine-pyrimethamine + amodiaquine (SPAQ).

Falsified and substandard products

Further reports of SF medical products related to Covid19 are being validating to determine if further alerts or updates are needed. There is a continued increase in websites suspected to offer SF medical products, in particular PPE. Member States and partner stakeholders have requested guidance on where and how to target market surveillance of specific products which are either affected by supply chain constraints or used in a clinical trial, as these may be at risk of SF.

The key messages of the general alert include the following, based on data available on 31 March: at this stage: www.who.int/medicines/publications/drugalerts/en/

- there are no mass-produced commercial diagnostic kits available yet
- WHO does not recommend any specific medicinal treatment for Covid19
- there are no existing vaccines to prevent Covid19, i.e., any product currently claiming to be a vaccine for Covid19 may be considered falsified

Alert on Falsified chloroquine products circulating in the WHO region of Africa, 09 April 2020
www.who.int/news-room/detail/09-04-2020-medical-product-alert-n4-2020

Medical Devices

Oxygen sources and distribution for COVID-19 treatment centres

This interim guidance, adapted from WHO and UNICEF's technical specifications, 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.

www.who.int/publications-detail/oxygen-sources-and-distribution-for-covid-19-treatment-centres

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 (not in priority order). It also describes alternative options that should be considered based on available infrastructure, health workforce and technologies. Please note some are capital equipment that requires accessories, spare part and extended warranties.

– Control click here to Access the document

Emergency global supply chain system catalogue

This catalogue lists all the medical devices including personal protective equipment, medical equipment, medical consumables, single use devices and laboratory and test related devices.

www.who.int/docs/default-source/coronaviruse/20200412-catalogue-v9.pdf?sfvrsn=ddd851d5_2

African Medical Devices Forum (AMDF) COVID-19 Task Force

African Medical Devices COVID-19 Task Force with the technical guidance from WHO has been meeting during the past two weeks and has generated the following for the African Regulators:

1. A list of Nucleic Acid tests (NAT) which have been authorized for Emergency Use to establish diagnosis of COVID-19 infection by WHO Prequalification, South Africa Health Products Regulatory Authority (SAHPRA), Pharmacy and Poisons Board (PPB) Saudi Arabia Food & Drugs Authority (SFDA), United States Food and Drug Administration (US FDA), Health Canada, Therapeutic Goods Administration (TGA), Health Sciences Authority (HSA) and the Ministry of Health, Labour and Welfare (MHLW) of Japan
2. A list of medical devices and personal protective equipment (PPEs) authorized by National Regulatory Authorities of Ghana, Nigeria, Kenya and Tanzania, ventilators and masks authorized by the US FDA and Health Canada as well as domestic manufacturers of medical devices and PPEs licensed in Tanzania and Kenya.
3. Standard operating procedure for handling complaints and reporting form for substandard and falsified medical devices including in vitro diagnostic tests.
4. Guidance on assessment of donations of medical devices including in vitro diagnostic tests for in country use during emergencies.

These documents will be shared extensively through the existing platforms such as AMDF MedNet and AUDA-NEPAD websites. The documents will also be translated into French, Arabic and Portuguese.

With the support of the WHO, AMDF COVID-19 Task Force will continue to meet and update the list for tests, medical devices, PPEs and domestic manufacturers as more information becomes available.

Regulatory Flexibility

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, and others will be listed in future updates. WHO will work with international regulators to develop best practices.

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
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
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

Sharing information by regional regulatory groups

The Pan American Network for Drug Regulatory Harmonization (PANDRA)

PAHO regularly shares information, in both Spanish and English, on COVID-19 regulatory actions in the Region available at the public level. Recent mailings include a warning of potential blood shortages during the COVID-19 pandemic, plus links to regulatory actions on COVID-19 by the NRAs of Argentina, Brazil, Canada, Chile and the USA.

For further information, please contact: pandrh@listserv.paho.org