



WHO Regional Office for Europe advice on the use of experimental  
medicines for the treatment of COVID-19 patients

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## Background

This advice was developed to address questions from Member States regarding the use of experimental medicines in the treatment of COVID-19 patients. It summarizes current WHO recommendations for the treatment of COVID-19 patients, information on the ethical and legal requirements for the use of experimental medicines in clinical trials (the WHO SOLIDARITY trial or other Randomized Control Trials (RCT)) as well as donated medicines, and the possible impact on global supplies of essential medicines for the treatment of non-COVID-19 patients where these drugs are included in COVID-19 clinical trials.

## WHO recommendations for the treatment of COVID-19 patients

WHO has published the guidance “Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected” This document is intended for clinicians taking care of hospitalized adult and paediatric patients with severe acute respiratory infection (SARI) when COVID-19 infection is suspected. Optimized supportive care should be provided to ensure the best possible chance for survival of COVID-19 patients as described in the WHO guidance:

1. Management of severe COVID-19 requires oxygen therapy and monitoring. Supplemental oxygen therapy should be given immediately to patients with SARI and respiratory distress, hypoxaemia or shock.
2. Management of critical COVID-19 (acute respiratory distress syndrome (ARDS)) requires advanced oxygen/ventilatory support.

[https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected<sup>\[1\]</sup>](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected<sup>[1]</sup>)

## Use of experimental drugs for the management of COVID-19 patients

There are currently no known effective or licensed treatment options for COVID-19. The public demand for identifying effective COVID-19 therapies to treat critically ill patients is leading many countries to initiate multiple small studies and compassionate use of candidate therapeutics of unknown or partially known effectiveness for treatment.

Globally randomized clinical trials are ongoing, including the WHO SOLIDARITY trial, but the use of these medicines for management of COVID-19 remains experimental. It is therefore critical that these medicines are provided under the safeguards of national regulations for clinical trials. All the medicines included in SOLIDARITY have known safety profiles for other conditions than COVID-19 and therefore may have significant side effects particularly when combined with other drugs. Robust pharmacovigilance and adverse event reporting are important. WHO teams are at your disposal to discuss the details. [eurosolidarity@who.int](mailto:eurosolidarity@who.int)

If conducting a randomized controlled trial (RCT) is not possible, then the use of all investigational therapeutics should be done under Monitored Emergency Use of Unregistered Interventions Framework (MEURI). WHO has issued a scientific brief on the off-label use of medicines for COVID-19. The paper stipulates that it can be ethically appropriate to offer individual patients experimental interventions on an emergency basis outside clinical trials, provided that: no proven effective treatment exists; it is not possible to initiate clinical studies immediately; the patient or his or her legal representative has given informed consent for the use of an experimental medicine with potential side-effects; and the emergency use of the intervention is monitored, including side-effects; and the results are documented and shared in a timely manner with the wider medical and scientific community. More details can be found here <https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19>

WHO is closely monitoring the evidence emerging from global research and regularly updating the technical guidance on COVID-19 patient management. Member states should use this to inform the development of national treatment protocols.

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management>].

## WHO Solidarity clinical trial on potential COVID-19 treatment options

The WHO Solidarity trial (SOLIDARITY) currently includes the following drugs: chloroquine or hydroxychloroquine; lopinavir and ritonavir; lopinavir/ritonavir plus interferon beta; and remdesivir. The experimental antiviral remdesivir, is not licensed for any indication. SOLIDARITY is an international randomized trial of in hospitalized patients who are all receiving the local standard of care. WHO would like to remind that the use of investigational anti-COVID-19 therapeutics (outside MEURI) should be done under ethically approved, randomized controlled trials (RCT) only. SOLIDARITY has an adaptive-design and therefore it is anticipated that additional medications will be added by WHO based on emerging evidence. WHO is facilitating access to thousands of free treatment courses for the trial through donations from many manufacturers. The effectiveness of the therapeutics included in the protocol, namely lopinavir/ritonavir, chloroquine phosphate, hydroxychloroquine, remdesivir, and interferon Beta 1a, must be demonstrated in RCTs before they can be considered for approval in clinical use in COVID-19 patients.

Remdesivir is not available for general procurement. It is an investigational drug, which can only be used in the context of phase III clinical trials. There has been some release on case by case basis for compassionate use by Gilead (producer). Since 23 March 2020, Gilead suspended access to remdesivir for compassionate use (excepting cases of critically ill children and pregnant women), for reasons related to supply, citing the need to continue to provide the agent for testing in clinical trials.

Other authorities, such as the European Medicines Agency (EMA), have issued advice that chloroquine and hydroxychloroquine are only to be used in clinical trials or emergency use programmes. Please consult the document at: <https://www.ema.europa.eu/en/news/covid-19-chloroquine-hydroxychloroquine-only-be-used-clinical-trials-emergency-use-programmes>.

WHO is monitoring the impact on supplies to treat malaria and working with suppliers to increase production.

## Non-SOLIDARITY Trial potential treatments

### **IL6/IL-1 antagonists**

An informal consultation on the potential role of IL6/IL-1 antagonists in the clinical management of COVID-19 infection was hosted in Geneva, Switzerland on 25th March 2020. Given the very limited evidence of the potential benefits of IL-6 inhibitors, including tocilizumab, the group agreed further work was required and commissioned a background paper to describe the rationale and justification for the inclusion of these therapies in an RCT. Therefore, at the

moment, there is an inconclusive opinion whether the use of IL6/IL1 antagonists in RCT is justified. The full report is available following the link [https://www.who.int/blueprint/priority-diseases/key-action/Expert\\_group\\_IL6\\_IL1\\_call\\_25\\_mar2020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Expert_group_IL6_IL1_call_25_mar2020.pdf?ua=1)

### **Favipiravir**

Favipiravir is an investigational drug which is not available for procurement and which can only be used in the context of phase III clinical trials. The manufacturers have launched a phase III trial in COVID-19 patients. To date it has only been licensed for influenza when other antiviral drugs are either not effective or insufficiently effective and animal experiments showed the potential for teratogenic effects. Its production and distribution are at the discretion of Japan's Health, Labor and Welfare Ministry, so has never been distributed in the market and is not available at hospitals and pharmacies in Japan or overseas.

UNOPS is currently assisting the Ministry of Foreign Affairs of Japan to distribute a donation of AVIGAN to 27 countries in the WHO European Region, which have requested the drug (Turkey, Luxembourg, Estonia, Bulgaria, Kosovo, Albania, San Marino, Kazakhstan, Slovenia, Georgia, Czech Republic, Poland, Hungary, Russia, Azerbaijan, Israel, Uzbekistan, Serbia, additional countries to be specified). UNOPS will be responsible for logistical facilitation, i.e. bringing the drug from the manufacturer in Japan to the respective Ministry of Health in the requesting country. Quantities are relatively small and aim to treat 100 potential patients in each country.

### **Convalescent Plasma**

WHO's guidance on the use of convalescent plasma states: "experience suggests that empirical use of convalescent plasma (CP) may be a potentially useful treatment for COVID-19. Detailed risk assessment must always be conducted to ensure that the blood service has sufficient capability to safely collect, process and store these specific blood components in a quality-assured manner" <https://apps.who.int/iris/rest/bitstreams/1272656/retrieve>

WHO has previously released interim guidance for the use of CP collected from patients recovered from Ebola Virus Disease. Additionally, the WHO Blood Regulators Network (<https://www.who.int/bloodproducts/brn/en/>)

Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus (2017) provides helpful considerations" [https://www.who.int/bloodproducts/brn/2017\\_BRN\\_PositionPaper\\_ConvalescentPlasma.pdf?ua=1](https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf?ua=1). The International Society of Blood Transfusion website has further COVID-19 specific resources [<http://isbtweb.org/index.php?id=1493>]

### **WHO Research and Development Blueprint**

As part of WHO's response to the outbreak, the WHO Research and Development Blueprint (R&D Blueprint) has been activated to accelerate research into diagnostics, vaccines, and therapeutics for this novel coronavirus. R&D Blueprint has been closely following the available evidence and

developments in the areas of novel therapeutics, vaccines and other measures for the management of COVID-19 cases through the involvement of a wide community of leading world scientists. The current updates on the research and development streams, including for prophylactic or post exposure prophylactic use can be accessed here [/https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov) <https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf>

## Global availability of essential medicines

It is inevitable that shortages of medicines for use in SOLIDARITY as well as in other RCT will occur before supply chains can adapt to meet global demand as countries are in the process of procuring the same products.

Moreover, Member States should ensure there are sufficient supplies of essential medicines needed for use in non-COVID patients with life-threatening conditions such as HIV and malaria, which are targeted for use in the SOLIDARITY trial as well as in other RCT.

Countries procurement of essential medicines for use in non-COVID-19 patients should be based on estimates of previous consumption. Stockpiling in large quantities will exacerbate the global situation.

## **The WHO Regional Office for Europe**

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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Cyprus  
Czechia  
Denmark  
Estonia  
Finland  
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Greece  
Hungary  
Iceland  
Ireland  
Israel  
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Latvia  
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