

# Public health emergency SOLIDARITY TRIAL

## World Health Organization COVID-19 core protocol

# SUMMARY

## An international randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care

**Version 10.0**
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## Summary

**Terminology:** The novel coronavirus-induced disease first described in 2019 in China is designated COVID-19 (or COVID), and the pathogen itself (an RNA virus) is SARS-coronavirus-2 (SARS-CoV-2).

**Background:** In early 2020 there were no approved anti-viral treatments for COVID, and WHO expert groups advised that four re-purposed drugs, Remdesivir, Lopinavir (given with Ritonavir, to slow hepatic degradation), Interferon (β1a), and chloroquine or hydroxychloroquine should be evaluated in an international randomised trial. WHO has provided guidelines that local physicians may consider when COVID-19 is suspected on clinical management of severe acute respiratory infection.

**Simplicity of procedures:** To facilitate collaboration even in hospitals that have become overloaded, patient enrolment and randomisation (via the internet) and all other trial procedures are greatly simplified, and no paperwork at all is required. Once a hospital has obtained approval, electronic entry of patients who have given informed consent takes only a few minutes. At the end of it, the randomly allocated treatment is displayed on the screen and confirmed by electronic messaging.

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

- Local standard of care alone,

OR local standard of care plus one of

- Remdesivir (daily infusion for 10 days)
- Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days)
- Lopinavir with Ritonavir (orally twice daily for 14 days)
- Lopinavir with Ritonavir (ditto) plus Interferon (daily injection for 6 days).

**Data reported before randomisation:** Information is entered electronically on

- Country, hospital (from a list of approved hospitals) and randomising doctor
- Confirmation that informed consent has been obtained
- Patient identifiers, age and sex
- Patient characteristics (yes/no): current smoking, diabetes, heart disease, chronic lung disease, chronic liver disease, asthma, HIV infection, active tuberculosis.
- COVID-19 severity at entry (yes/no): shortness of breath, being given oxygen, already on a ventilator, and, if lungs imaged, major bilateral abnormality (infiltrations/patchy shadowing)
- Whether any of the study drugs are currently NOT AVAILABLE at the hospital.

**Exclusion from study entry:** Patients will not be randomised if, in the view of the randomising doctor, ANY of the AVAILABLE study drugs are contra-indicated (eg, because of patient characteristics, chronic liver or heart disease, or some concurrent medication).

**Changing management of study patients:** At all times the patient's medical team remains solely responsible for decisions about that patient's care and safety. Hence, if the team decide that deviation from the randomly allocated treatment arm is definitely necessary, this should be done.

**Follow-up:** When patients die or are discharged, follow-up ceases and it is reported:

- 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.

If no report is received within 6 weeks of study entry, an electronic reminder is sent.

**Drug safety:** Suspected unexpected serious adverse reactions that are life-threatening (eg, Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia, or anything comparably uncommon and serious) must be reported within 24 hours of being diagnosed, without waiting for death or discharge.

**Major outcomes:** The primary outcome is all-cause mortality, subdivided by severity of disease at the time of randomisation. The major secondary outcomes are duration of hospital stay and time to first receiving ventilation (or intensive care).

**Data monitoring:** A global Data and Safety Monitoring Committee will keep the accumulating drug safety results and major outcome results under regular review.

**Numbers entered:** The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops. If substantial numbers get hospitalised in the participating centres, it may be possible to enter several thousand hospitalised patients with relatively mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial and will depend on the evolution of the epidemic.

**Heterogeneity between populations:** If a study treatment does affect outcome, then this effect could well differ between patients who had severe disease when randomised and those who had less severe disease. It could also differ between younger and older patients, or between patients in one or another country. If sufficient numbers are randomised, it may be possible to obtain statistically reliable treatment comparisons within each of several different countries or types of patient.

**Adaptive design:** The WHO may decide to add novel treatment arms while the trial is in progress. Conversely, the WHO may decide to discontinue some treatment arms, especially if the Global Data and Safety Monitoring Committee reports, based on interim analyses, that one of the trial treatments definitely affects mortality.

**Add-on studies:** Particular countries, or particular groups of hospitals, may want to collaborate in making further measurements or observations, such as serial virology, serial blood gases or chemistry, serial lung imaging, or serial documentation of other aspects of disease status (eg, through linkage to 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.

**Data security:** Patient information will be encrypted and held securely by the WHO. Those analysing it will use only anonymised data, and no identifiable patient details will appear in publications.

**Publication:** This international collaboration is co-ordinated through the World Health Organisation. Any wholly reliable interim findings on mortality will be disseminated rapidly by the WHO and will be published in the names of the collaborators.

# Overview of study procedures within hospitals

To facilitate collaboration, even in hospitals with many patients, all trial procedures are simplified, and no paperwork is required. Within each country, the national co-ordinator invites selected hospitals to join and helps them get ethical approval and supplies of the study drugs (SOP-1). Once an invited hospital has ethical approval and its pharmacy has some or all of the study drugs, patient entry can begin.

| | Procedures within collaborating hospitals |
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| 1 | **Provisional eligibility** Eligible patients are adults (age ≥18 years) recently admitted as inpatients, or already in hospital, with definite COVID-19 for whom the responsible doctor would be willing to initiate any of the study treatment arms that might be allocated. |
| 2 | **Consent** The study website **www.who.int/COVIDcore** has printable patient information in local languages, inviting consent to join the study. If laboratory confirmation is not yet available, the information required for consent can be provided to the patient in preparation for when laboratory results do emerge.<br><br>Once the information has been explained, obtaining consent takes only a few minutes, as the signature process is easy. An electronic image of the signature page is kept, and printed information and original consent stays with the patient, isolated from study staff. |
| 3 | **Patient details** Enter the following information onto **www.who/COVIDcore**<br>- Country, hospital (from an electronic list), and email of randomising doctor<br>- Confirmation that informed consent has been obtained<br>- Patient identifiers, including admission date, age and sex<br>- Patient characteristics (each yes/no): Smoking? Diabetes? Heart disease? Chronic liver disease? Chronic lung disease? Asthma? HIV infection? Active TB?<br>- COVID-19 severity (each yes/no): Shortness of breath? On oxygen? Already ventilated? and, if lungs imaged, major bilateral abnormality? (infiltrations/patchy shadowing) |
| 5 | **Drug availability, and random allocation**<br>- List which of the 5 study drugs are currently available in this hospital (5 yes/no answers, although chloroquine is asked about only if hydroxychloroquine is not available)<br>- Confirm this patient has no contra-indications to any of these available drugs (1 answer)<br><br>A study ID for the patient is then generated and displayed, and the random allocation (to something available) is displayed and confirmed by electronic messaging.<br>This patient is now in the study, and their in-hospital outcome will be sought. |
| 6 | **Trial treatment** If the random allocation includes study medication, then that medication should begin promptly, and continue daily until completed, or until the responsible physician decides it should stop.<br><br>Any suspected serious adverse reaction is reported within 24 hours, using patient's study ID. |
| 7 | **Follow-up** At discharge or death, log into **www.who/COVIDcore** and enter<br>- The patient's study ID<br>- Which study drugs were given (and for how many days)<br>- Whether ventilation or intensive care was received (and, if so, when)<br>- Date of discharge, or date and cause of death.<br><br>If follow-up information is not received within 6 weeks of patient entry, a reminder is sent. |