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Public health emergency SOLIDARITY TRIAL

World Health Organization COVID-19 core protocol

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

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Protocol signature page

Reviewed and approved by the following representatives of the Co-Sponsors :

Signature.....
Representative of the National Ministry of Health

Print name and position _____

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Date_____

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Representative of the World Health Organization (WHO)

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Date_____

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	SOP
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. 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.	SOP-2
3	**Patient details** Enter the following information onto **www.who/COVIDcore** - Country, hospital (from an electronic list), and email of randomising doctor - Confirmation that informed consent has been obtained - Patient identifiers, including admission date, age and sex - Patient characteristics (each yes/no): Smoking? Diabetes? Heart disease? Chronic liver disease? Chronic lung disease? Asthma? HIV infection? Active TB? - 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** - 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) - Confirm this patient has no contra-indications to any of these available drugs (1 answer) 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. 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. Any suspected serious adverse reaction is reported within 24 hours, using patient's study ID.	SOP-4 to 7
7	**Follow-up** At discharge or death, log into **www.who/COVIDcore** and enter - The patient's study ID - Which study drugs were given (and for how many days) - Whether ventilation or intensive care was received (and, if so, when) - Date of discharge, or date and cause of death. If follow-up information is not received within 6 weeks of patient entry, a reminder is sent.	SOP-8

Objectives

The aim of this core protocol is to compare the effects on major outcomes in hospital of the local standard of care alone *versus* the local standard of care plus one of four alternative anti-viral agents.

The primary objective of this large international randomised trial is to provide reliable estimates on any effects of these anti-viral treatments on in-hospital mortality in moderate and in severe COVID.

The secondary objectives are to assess any effects of these anti-viral treatments on hospital duration and receipt of ventilation or intensive care, and to identify any serious adverse reactions.

It is not expected that any of the treatments currently being tested will have a large effect on the risk of death, but if any had just a moderate effect and was widely practicable then this could avoid large numbers of deaths. Conversely, reliable demonstration that certain agents have no material effect on major outcomes would be of value. Moderate effects can, however, be reliably demonstrated or refuted only by large-scale randomized evidence.

Study population: inclusion, exclusion, and recruitment

Eligibility: consenting adults (age ≥18) hospitalised with definite COVID-19, not already receiving any of the study drugs, without known allergy or contra-indications to any of them (in the view of the physician responsible for their care), and without anticipated transfer within 72 hours to a non-study hospital. Patients invited to join the study will be those who are admitted to a collaborating hospital; no wider recruitment efforts are expected.

A patient is not eligible for the trial if believed by their physician to have a significant contra-indication to any one of the study drugs (eg, serious chronic liver or heart disease or pregnancy)

Study products and study drug regimens

Four potential anti-viral agents, Remdesivir, Chloroquine/Hydroxychloroquine, Lopinavir (given with Ritonavir, to slow hepatic degradation) and Interferon (β1a) are to be evaluated (see SOPs-4 to 7b).

Preparation, handling, storage and, accountability

Study drugs will be shipped to the site either directly from participating companies, or from other regional or local drug repositories. All other supplies will be provided by the site. The site principal investigator is responsible for study drug disposition and product accountability (see SOPs-4 to 7b).

Formulation, stability, labelling, storage and preparation of study products

See SOP-4 to SOP-7b for details of each of the study products.

Drug discontinuation and patient withdrawal

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

The study drug administration must be stopped if the team suspects any serious unexpected drug-related reaction that is life-threatening.

Patients are free to withdraw from study treatment at any time, but could still remain in the study, with in-hospital outcome reported to the study at death or discharge.

Patients are also free to withdraw from the whole study at any time without any consequence and would continue to be offered the local standard of care (but not be reported on).

Randomisation

Patients will be randomised through the study website equally between all the locally available treatment regimens (5 possibilities if all study drugs are locally available, fewer if not – see SOP 2):

- 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)
  [NB Some collaborating hospitals will study chloroquine, others hydroxychloroquine]
- Lopinavir with Ritonavir (orally twice daily for 14 days)
- Lopinavir with Ritonavir (ditto) plus Interferon (daily injection for 6 days).

Adverse reaction reporting

Any serious unexpected adverse reaction that is life-threatening (e.g. anaphylaxis, Stevens-Johnson syndrome, aplastic anaemia, or anything comparably strange) must be reported through the study website within 24 hours. Such complications should be extremely rare, and there is no good reason to expect the trial treatments will cause them, so many hospitals will never make such a report (SOP 9).

Statistical considerations

Analyses relate outcome to the randomly allocated treatment (ie, intent-to-treat). The primary analyses assess any effects of treatment allocation on all-cause in-hospital mortality, analysing separately people who already had severe disease at entry and those who did not.

The main secondary analyses assess any effects of treatment allocation on the duration of hospitalization (time from randomisation to discharge) and need for ventilation or intensive care.

Sample size

No specific sample size is specified in this public health emergency core protocol. Interim results will be kept under review by an independent Global Data and Safety Monitoring Committee, and this Committee will decide how often to conduct interim analyses. It is anticipated that at least several thousand patients will be recruited into the trial.

The larger the numbers entered the more accurate the results will be, but the numbers that can be entered will depend critically on how large the epidemic becomes. If substantial numbers of patients are hospitalised in the participating centres then it may be possible to enter several thousand hospitalised patients with relatively mild disease when admitted and a few thousand admitted with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial. Another reason for entering large numbers is that the response to certain treatments may differ substantially between different populations or sub-populations (eg, patients with particular prior conditions, older adults, patients in one or another large 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.

Study assessments and procedures

Schedule of assessments

	At recruitment	During hospitalization	At death or hospital discharge
ELIGIBILTY			
Definite confirmation of COVID-19	X		
Informed consent	X		
RANDOMIZATION			
Enter into www.who.int/COVIDcore patient identity, concomitant conditions, and severity of disease	X		
The study issues a patient study number, and a random treatment allocation	X		
STUDY INTERVENTION			
Administer any anti-viral agents specified by the random allocation, unless the local doctors decide for any reason to stop		Daily for 6-14 days, unless discontinued	
Report any serious and unexpected adverse reactions to study website		Report promptly within <24 hours	
REPORTING OUTCOMES			
Enter into www.who.int/COVIDcore in-hospital treatment (study drug, ventilation, duration of stay) and, if died in hospital, cause of death			X
Reminder sent if outcome (or study withdrawal) not already reported within 6 weeks			(Reminder 6 weeks after study entry)

Regulatory, ethical, and study oversight considerations

This study will be conducted in conformity with the principles of ICH E6(R2). When local ethics committees review this international protocol, it can be approved (after which the study can proceed at that locality) or rejected (in which case it will not proceed) but cannot be altered. Likewise, any substantial amendments made centrally to the core protocol or consent procedure while the trial is in progress can only be approved or rejected by local ethics committees.

Informed Consent Process

Eligible patients will receive a concise description of the study, verbally and in writing. If they wish to join, they must sign their consent electronically beforehand. An electronic image of their signature is retained, but the patient retains the hard copy of the information and consent (SOP 2).

Confidentiality and Privacy

Patient confidentiality is held in trust by the investigators. No identifiable information will be released to any unauthorized third party. All study data will be encrypted for analysis. Patient confidentiality will be maintained when study results are disseminated.

Key Roles and Study Governance

Interim trial analyses are monitored by a Global Data and Safety Monitoring Committee (Appendix 1 - Global Data and Safety Monitoring Committee).

Otherwise, the WHO, collaborators, and administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results.

The evidence on mortality must be strong enough and the range of uncertainty around the results must be narrow enough to affect national and global treatment strategies.

The Global Data Monitoring and Safety Committee will independently evaluate these analyses and will inform the Executive Group of the Steering Committee if at any stage the results are sufficiently robust for general release and for affecting global recommendations.

The trial governance is described in Appendix 2.

Monitoring protocol compliance

Monitoring to ensure that trial patients are protected, and the reported trial data are timely and complete will be conducted mainly by central data checks, not by site visits (which are avoided, partly to limit spread). Monitoring will be implemented in compliance with international regulations.

Source records and study record retention

Source data are all electronic. Study-related records, product accountability records, and informed consent records will be maintained for at least 5 years after the investigation is discontinued. If, before or during that period, this study is used in a marketing application for any study drug, then the records will be kept for at least 5 years after that application is approved or rejected. No records will be destroyed without the written consent of the WHO, acting in its role as sponsor of the trial.

Protocol Deviations

As the protocol leaves the local doctor fully responsible for all decisions about patient care, including the possibility of discontinuing study medication if this is considered appropriate, the only possible major protocol deviation would be substantial over-dosing with a study drug. If this happens, it should be reported within 24 hours on the study website.

The DSMC chair will then decide whether this constitutes a sufficiently major protocol deviation for it to need to be forwarded promptly to the relevant national co-ordinator and to any relevant ethics committee.

Sponsorship, and management of conflicts of interest

In each country the Co-Sponsors of this study are the National Ministry of Health and the World Health Organisation. The study drugs will be available at no cost from the study Sponsors, but the study does not cover any other aspect of patient care.

The independence of this study from any actual or perceived financial influence, such as from pharmaceutical companies or their consultants, is critical. Therefore, any conflicts of interest in its design, conduct, analysis, interpretation or publication, will be disclosed and managed by the WHO and the national Co-Sponsor.

Data sharing

After the trial has ended and its results have been reported, anonymized data sharing will occur as per the Policy Statement on Data Sharing by the World Health Organization.

Publications

This international collaboration is co-ordinated through the World Health Organisation, which is also a sponsor of the trial. Any wholly reliable interim findings will be disseminated rapidly by the WHO. There will be group authorship recognizing the contribution of all national and local investigators and guided by the International Committee of Medical Journal Editors (ICMJE) recommendations.

Insurance

WHO has established a global liability insurance (for individuals suffering serious adverse reactions arising from the use of the investigational therapeutics for COVID-19 as part of the Solidarity Trial) that will cover all countries that participate in the Trial.

In its agreement with WHO, and as a condition to receive the investigational therapeutics for use in the Solidarity Trial, the countries participating in the Solidarity Trial will be required to indemnify WHO, donors and the manufacturers of the investigational therapeutics. In exchange, WHO will - through the above-mentioned insurance - facilitate access to compensation for individuals suffering from serious adverse reactions arising from the use of the investigational therapeutics in the Solidarity Trial.

This insurance provides a mechanism to compensate individuals suffering from serious adverse reactions arising from the use of the study drugs. A lump sum will be offered as a no-fault compensation in full and final settlement of any claims.

In addition, the insurance provides a certain level of liability insurance for: (i) the manufacturers supplying the investigational study drugs for use in the Trial; (ii) WHO; and (iii) any person and organization collaborating with WHO in assisting the recipient government with the Trial (including donors). Coverage is triggered when a person refuses the lump-sum compensation provided for by the insurance. This would contribute to the costs of defending claims and the payment of compensation, if awarded.

In principle, coverage is provided for serious adverse reactions following the use of an unlicensed therapeutic in all countries, except the OECD, EFTA (Norway, Switzerland, Iceland and Liechtenstein) and the European Union. In other words, in principle, coverage is provided for individuals in all countries to which WHO may distribute unlicensed therapeutics. The territorial scope of the policy (for the filing of claims) is worldwide. Compensation covered by the insurance would be paid directly to the individuals concerned.

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