Public health emergency SOLIDARITY TRIAL

World Health Organization

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

Standard Operating Procedures and Appendixes

Version 9.0
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SOP-1 Approval of hospitals to join the trial and access trial drugs

If the WHO Director-General asks the Minister of Health of a seriously affected country, and the Minister decides the country should join the trial, two high-level representatives are chosen, one of the Health Ministry (or Medical Research Council) and one of the a leading clinical investigators. These two National Representatives will work together to get all necessary approvals rapidly, to select as potential collaborating centres major hospitals that already have, or are expected soon to have, substantial numbers of inpatient admissions for COVID, and to facilitate local ethical approval on behalf of willing local collaborators. The following steps should ensure the trial can start promptly in each collaborating hospital. They should happen in parallel, and not in sequential fashion.

Step	What?	Who?	How?	Remarks
1	Officially confirm interest to participate	Minister of Health or authorised Delegate of the Minister of Health	Communication to WHO Secretariat solidaritytrial@who.int	
2	Appoint two National Representatives, one Governmental and one Clinical	Within-country choice by Ministry of Health or main Research Council and a leading clinical investigator	Communication to WHO Secretariat solidaritytrial@who.int	These two National Representatives should both be senior within their Ministry or profession
3	Identify which hospitals will have substantial numbers and will collaborate	The two National Representatives, with one lead doctor per selected hospital	Communication to WHO Secretariat solidaritytrial@who.int	Selected hospitals should have basic GCP knowledge
4	Facilitate approval - or not - by national authority and local ethics committees	The two National Representatives.	High-level national decisions, not just local applications by each collaborator	No modification of the protocol is possible, as very large numbers of hospitals are involved.
5	Establish which study drugs are available in each location	Clinical National Representative, helped by WHO focal point	Bilateral interactions	WHO will facilitate study drug provision where this is needed
6	Facilitate import permits for study drugs, as pertinent	The two National Representatives.	Depends on national guidelines and regulations	After permits for initial amounts, resupply will depend on entry rate
7	Set up personnel and logistics for study implementation	Appoint small central administrative staff for the Clinical National Representative	Make use of existing p.a. and other staff of known reliability to disseminate study	Local centres will need help on approvals, drug supplies, getting going, and maximising accrual
8	Within local hospitals, move quickly into rapid recruitment	Lead doctor and lead pharmacist motivate and train colleagues	Local leads explain and discuss study with colleagues	Local lead motivates & ensures full compliance, rapid entry and discipline

SOP-2 Access to global enrolment and randomization center

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.

Access is via the WHO study website www.who.int/COVIDcore

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.

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 electronic signing process is easy. The printed information and consent stays with the patient.

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)

Drug availability, and random allocation
- List which of the 4 study drugs are currently available in this hospital (4 yes/no answers)
- 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.
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.

SOP-3 Informed consent form

Principal Investigator	
Study Sponsor	
Name of protocol and version	

Coronavirus-induced disease (COVID-19, or COVID) Informed consent to join the WHO Solidarity randomised trial

To the health worker: No drugs are of proven value against COVID-19, and we are therefore inviting hospitalised adults older than18 years to consent to join a research study. All who participate will receive the usual care offered in this hospital, and in addition some but not all will be given one extra treatment chosen at random from a few untested treatments. The aim is to discover whether any of these treatments slows disease progression or improves survival.

To the patient: You have a lung disease called COVID. Several medicines for it have been proposed. These medicines may have no effect or a moderate effect on the disease, but none is expected to have a big effect. This hospital is collaborating through the World Health Organization and hospitals in many other countries in a study to help discover whether any of these treatments can help.

Whether or not you choose to join, you will still receive the usual standard of care at this hospital. If you do not join the study you will receive whatever your doctor thinks is best.

If you decide to join, you may receive one untested treatment chosen by chance, as if on the roll of a dice.

This form has two parts:
1. To share information about the treatments being tested.
2. For your signature, if you do decide to take part

PART 1: Information Sheet

Introduction
I am _____, working for the _____.

You have a lung disease called COVID that recently spread across the world. Most people recover fully from COVID, but a few die. This hospital is collaborating in an international research study to help discover whether some untested treatments could help treat COVID. I am going to tell you about the study, then invite you to join it. Before you decide, you can talk to anyone about it. If there are any words you don't understand, please ask me to stop and explain. If you have questions later, I'll be available to answer them, and so will the study doctors.

Purpose of the research
The disease is called COVID-19 because it was first discovered in 2019, but I'll just call it COVID. It's caused by a new virus that can be passed between people touching or through the air when an infected person coughs or sneezes, so the hospital staff wear protective clothing. Most people with COVID get better without coming to hospital, and most who come to hospital also get better, although they may get worse before they get better. But, a few of those in hospital die from the illness.

There are currently no licensed vaccines or treatments for COVID. Although treatments for other diseases might be of some help, they might not. The World Health Organization is therefore organizing a study in many countries in which some of these treatments are compared with each other, to see whether they are of any use for treating COVID.

The study treatments are listed briefly below. Some are given as daily pills, and some as daily injections. During the study some treatments may get removed from this list, and others may get added to it. Each patient will receive at most one of the treatments.

Invitation to participate
Adults admitted to this hospital with COVID can join this study. If you join, you will be asked to sign that you understand that there are possible risk and benefits and consent to join the study. Your doctor will check whether you are eligible to join, and whether any of the study treatments would definitely be unsuitable for you.

After those checks, brief details identifying you and any other conditions you have are put into the computer, and you are then randomly allocated to one of the study options. This may or may not involve one of the study treatments. Neither you nor the medical staff can choose which of the study options you will receive, as the computer makes this allocation at random, as if on the roll of a dice.

Any study treatment should start promptly and continue for about ten days, unless you or your doctor decide for any reason that it should stop. In addition, you will still receive what is already being done for COVID patients in this hospital. No additional visits after you leave the clinic/hospital are required. You or our doctor can stop the untested treatment at any time before it has been completed and you are free at any time to change your mind and stop participating.

Joining is voluntary and will not affect the care you receive at this hospital. You will not be paid for your participation, and neither will the medical staff. But, you will not have to pay for the study treatment itself. Your identifying details will be shared confidentially with international researchers, along with information about the course of your illness, and we would need to use your identifying details to link your treatment to your future medical records for long enough to know whether you are properly cured. The findings will be made freely available worldwide to help future patients, but your details will not be identifiable.

I've got a list describing briefly the possible side-effects of each of the study drugs. We could either read it now, or you could join the study, find out immediately whether you'd be taking one of these drugs and then just learn about that one and decide whether or not you want to take it.

Risks and benefits
Any study treatment you receive may or may not help you personally, but this study could help future patients.

This study has been reviewed and approved by _____, a committee (contact details) set up to make sure research participants are protected.

Some of the study treatments are given as daily pills, and some as daily injections. They have been used safely in other diseases, although a few people have had temporary side effects. With any drug there is the unlikely possibility of an unexpected severe reaction to it.

Remdesivir is made by Gilead. Its side effects are not common or serious, and last only a few days. These involve digestive discomfort (such as loss of appetite, heartburn, feeling sick or being sick, loose stool or constipation) or general discomfort (such as trembling, itching, headache, dizziness or unusual feelings in the ear). Some patients' blood tests show changes in how well the kidney or liver is functioning, but these stop when the drug is stopped.

Lopinavir is made by Company _____. It is given with Ritonavir, which prevents the liver breaking down the Lopinavir too quickly. Some users feel sick, are sick, or have diarrhoea. Long-term use to treat HIV disease can increase the amount of cholesterol and other fats in the blood, but that wouldn't matter in short-term treatment.

Interferon is made by Merck Sharp and Dohme. Flu-like symptoms are common but usually fairly mild. It is given by daily injection, and sometimes the injection site becomes swollen or sore, but this gets better after treatment ends. Some patients' blood tests show changes in how well the liver is functioning, but these stop when the drug is stopped. Some interferon users had episodes of depression and even thought of suicide, so you should not have this drug if you ever had serious depression, or attempted suicide.

Chloroquine and hydroxychloroquine are old, widely used anti-malaria drugs that are made by many companies. They may cause digestive discomfort (stomach pain, feeling sick or being sick), itching or mild dizziness. You should not take them if you have seizures, epilepsy, or serious hearing or visual problems (not just needing hearing aids or reading glasses There have been rare heart problems, so those with serious heart disease are not invited into the study.

PART II: Certificate of consent

Clinic/Hospital : **City/Town:**

Province/Region: **Country:**

Participant: I read the information, or had it read to me. I could ask any questions I wanted, and had any questions answered satisfactorily. I consent voluntarily to participate in this study.	**Literate Witness (if participant is illiterate):** I witnessed the information sheet being read accurately. The participant could ask any questions and got satisfactory replies. I confirm that they gave their consent freely.
First & last name	**First & last name**
Signature	**Signature**
Date	**Date**
Thumb-print (if illiterate*)	

**Illiterate participants include their thumbprint, and a literate witness counter-signs the form .*

Statement by the researcher/person taking consent

I accurately read the information sheet to the participant and made sure they understand what the study entails. The participant could ask questions about the study, and all questions asked were answered correctly to the best of my ability. Consent was given freely and voluntarily, and a copy of this form has been given to the participant.

Person taking the consent:	
First & last name	
Signature	
Date	

This study has been reviewed by ethics experts at the World Health Organization (WHO), which is co-sponsoring it. The study has been reviewed and approved locally by _____ .This committee exists to make sure research participants are protected from harm. If you want to contact them about it, now or later, their contact details are _____ .

SOP-4 Pharmacy manual Remdesivir (investigational antiviral)

1. Drug product

The lyophilized formulation of Remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 100 mg of Remdesivir to be reconstituted with sterile water for injection and diluted into IV infusion fluids prior to IV infusion. It is supplied as a sterile product in a single-use, 50 mL, Type 1 clear glass vial. In addition to the active ingredient, the lyophilized formulation of Remdesivir contains the following inactive ingredients: water for injection, SBECD, hydrochloric acid, and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide are used to adjust the formulation to a final pH of 3.0 to 4.0 following reconstitution.

2. Drug receipt

Ambient vials of the lyophilized formulation of Remdesivir must be shipped below 30°C. Upon receipt, the recipient should check all vials and ensure no vials are broken. If vials are broken, the vials should be discarded. Receipt and accountability of the product on site should be documented and the appropriate persons notified according to the study procedures.

3. Storage and handling

Ambient vials of the lyophilized formulation of Remdesivir should be stored below 30°C. Storage within a separately locked room is preferable but not essential. Temperature records must be maintained by the site to demonstrate drug was stored appropriately.

4. Dose preparation

The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids (Normal Saline) before use. After reconstitution, the total storage time before administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C).

Study doses are 200 mg (2 vials) intravenous loading dose on Day 1, and 100mg (1 vial) intravenous once-daily for subsequent doses from Day 2 up to Day 10.

The total volume of administration can be 250mL or 500ml of Normal Saline. The infusion can be administered between 30 minutes and 2 hours.

5. Disposition of unused product

Records of doses dispensed should be kept and provided to study staff on request. If any un-opened, study packages remain at the end of the study the local study PI should be contacted for further instructions regarding the disposition of these vials.

Opened, partially unused packages should be destroyed at study end in consultation with study staff after proper accountability has been performed.

6. Maintenance of inventory logs

Use of doses should be tracked and recorded on drug disposition logs for use during accountability procedures by study staff. Records of when doses were dispensed or destroyed must be kept in these logs.

7. Emergency contact

In the event of an emergency or the need for immediate information regarding product preparation, handling, storage or administration, contact the study's local investigator.

SOP-5 Pharmacy manual Lopinavir/Ritonavir (off-label use, antiviral)

1. Drug product

Lopinavir/ritonavir is available from multiple manufacturers as fixed dose co-formulated heat-stable tablets for oral administration: 200mg lopinavir with 50 mg ritonavir per tablet.

The oral solution for patients who cannot swallow is a light yellow to orange colored liquid containing 400 mg lopinavir and 100 mg ritonavir per 5 mL (80 mg lopinavir and 20 mg ritonavir per mL).

2. Drug receipt

Lopinavir/ritonavir heat stable tablets are shipped at room temperature.
Lopinavir/ritonavir oral solution is shipped at 2°- 8°C.

Upon receipt, the recipient should check the integrity of the package. If packages are broken they should be discarded. Receipt and accountability of the product on site should be documented and the appropriate persons notified according to the study procedures.

3. Storage and handling

Lopinavir/ritonavir tablets should be stored at room temperature 20°- 25°C, excursions are permitted to 15°- 30°C, (less than 30 degrees C) in a locked container which is only used for Solidarity protocol drugs. Storage within a separately locked room is preferable but not essential.

Lopinavir/ritonavir oral solution should be stored at 2°- 8°C until dispensed and exposure to excessive heat should be avoided. If stored at room temperature up to 25°C, oral solution should be used within 2 months.

Temperature records must be maintained by the site to demonstrate drug was stored appropriately.

4. Dose preparation

The recommended standard dosage of tablets is 400 mg lopinavir /100 mg ritonavir (two 200/50 mg) tablets twice daily every 12 h for 14 days taken with or without food.

Where the patient is unable to take oral tablets, a 5-mL suspension is available which can be given via nasogastric tube every 12 h for 14 days.

5. Disposition of unused product

Records of doses dispensed should be kept and provided to study staff on request. If any un-opened, study packages remain at the end of the study the local study PI should be contacted for further instructions regarding the disposition of these vials.

Opened, partially unused packagers should be destroyed at study end in consultation with study staff after proper accountability has been performed.

6. Maintenance of inventory logs

Use of doses should be tracked and recorded on drug disposition logs for use during accountability procedures by study staff. Records of when doses were dispensed or destroyed must be kept in these logs.

7. Emergency contact

In the event of an emergency or the need for immediate information regarding product preparation, handling, storage or administration, contact the study's local investigator.

SOP-6 Pharmacy manual Interferon beta-1a (off-label use, immunomodulator)

1. Drug product

Interferon ß1a is supplied as a sterile solution containing no preservative available in a prefilled syringe. It is provided as a single-dose prefilled graduated syringe available in two concentrations; either with 44 micrograms per 0.5 mL OR 22 micrograms per 0.5 mL. The liquid should be clear to slightly yellow. Do not use if the liquid is cloudy, discolored or contains particles. Use a different syringe. It contains the following inactive ingredients: albumin (human), mannitol, sodium acetate, water for injection.

2. Drug receipt

Interferon Beta1a is shipped at 2°C to 8°C. Upon receipt, the recipient should check the integrity of the package. If packages are broken they should be discarded. Receipt and accountability of the product on site should be documented and the appropriate persons notified according to the study procedures.

3. Storage and handling

Interferon Beta1a is stored at 2°C to 8°C. Do not store in a freezer compartment. The study drug must not freeze. It should be stored in its original packaging protected from light.
Interferon Beta1a should be stored at 2°C to 8°C in a locked container which is only used for Solidarity protocol drugs. Storage within a separately locked room is preferable but not essential. If needed, IFN ß-1a may be stored between 2°C to 25°C for up to 30 days and away from heat and light, but refrigeration is preferred.
Temperature records must be maintained by the site to demonstrate drug was stored appropriately.

4. Dose preparation

When patients require non-invasive ventilation OR high flow oxygen devices OR invasive mechanical ventilation OR ECMO:

- Interferon ß-1a will be administered intravenously at the dose of 10-µg once daily. No dosage adjustment is provided for renal or hepatic impairment for Interferon ß-1a.

When patients do not require non-invasive ventilation NOR high flow oxygen devices NOR invasive mechanical ventilation NOR ECMO:

- Interferon ß1a will be administered subcutaneously at the dose of 44 µg 3 times weekly at the same time, i.e. on Day 1, Day 3 and Day 6. No dosage adjustment is provided for renal or hepatic impairment for Interferon ß-1a.

The duration of treatment with interferon ß-1a whether IV or subcutaneous will be 6 days.

5. Disposition of unused product

Records of doses dispensed should be kept and provided to study staff on request. If any un-opened, study packages remain at the end of the study the local study PI should be contacted for further instructions regarding the disposition of these vials. Opened, partially unused packagers should be destroyed at study end in consultation with study staff after proper accountability has been performed.

6. Maintenance of inventory logs

Use of doses should be tracked and recorded on drug disposition logs for use during accountability procedures by study staff. Records of when doses were dispensed or destroyed must be kept in these logs.

7. Emergency contact

In the event of an emergency or the need for immediate information regarding product preparation, handling, storage or administration, contact the study's local investigator.

SOP-7a Pharmacy manual Chloroquine phosphate (off-label use, antiviral)

1. Drug product

Chloroquine phosphate is available from multiple manufacturers as heat-stable tablets for oral administration, each containing 250 mg chloroquine phosphate. (250 mg chloroquine phosphate corresponds to 155 mg chloroquine free base.)

2. Drug receipt

Chloroquine phosphate heat-stable tablets can be shipped at room temperature, and can be locally sourced if supplies shipped by the WHO Solidarity study are not available. If the Solidarity study supplies the drug then, upon receipt, the recipient should check the integrity of the package, and if packages are broken they should be discarded. Receipt and accountability of study-supplied product on site should be documented and the local lead pharmacist should ensure continuity of availability on site of study-supplied or of locally sourced 250 mg chloroquine phosphate tablets

3. Storage and handling

Chloroquine phosphate tablets should be stored at room temperature (under 30 degrees C). If supplied by the study then they should be kept in a locked container which is only used for Solidarity protocol drugs. Storage of study drug within a separately locked room is preferable but not essential. Temperature records should be maintained to demonstrate that the tablets were stored appropriately

4. Doses

The tablets can be taken with or without food. There are two loading doses (each of 4 tablets) and 20 maintenance doses (each of 2 tablets).

The two loading doses are scheduled to be given 6 hours apart. The maintenance doses are scheduled to begin 6 hours after the second loading dose and to be given 12 hours apart. Hence, the final maintenance dose is scheduled to be given 10 days after the first loading dose.

5. Disposition of unused product

Records of doses dispensed should be kept and provided to study staff on request. If any unopened study-supplied packages of the drug remain when the local lead clinician informs the local lead pharmacist that the study has ended, the pharmacist will inform the lead clinician what supplies remain.

The local lead clinician will then decide on their disposition. Unless there are good reasons otherwise, opened but partially unused packages of study-supplied drug should be destroyed at the end of the study, with proper accountability shared

between the local lead pharmacist and the local lead clinician for all study-supplied drug ever received.

6. Maintenance of inventory logs

Use of study-supplied drug should be tracked and recorded on drug disposition logs in case they are required later (as, for example, during post-trial drug accountability checks for the study). Records of when study-supplied doses were dispensed or study-supplied product was destroyed should be kept in these logs.

7. Emergency contact

In the event of an emergency or the need for immediate information regarding product preparation, handling, storage or administration, the local study pharmacist and the local lead clinician should consult together. This product has been in wide use for many years for other indications, so there is extensive experience with it.

SOP-7b Pharmacy manual Hydroxychloroquine sulphate (off-label use, antiviral)

1. Drug product

Hydroxychloroquine sulphate is available from multiple manufacturers as heat-stable tablets for oral administration, each containing 200 mg hydroxychloroquine sulphate. (200 mg hydroxychloroquine sulphate corresponds to 155 mg hydroxychloroquine free base.)

2. Drug receipt

Hydroxychloroquine sulphate heat-stable tablets can be shipped at room temperature, and can be locally sourced if supplies shipped by the WHO Solidarity study are not available. If the Solidarity study supplies the drug then, upon receipt, the recipient should check the integrity of the package, and if packages are broken they should be discarded. Receipt and accountability of study-supplied product on site should be documented and the local lead pharmacist should ensure continuity of availability on site of study-supplied or of locally sourced 200 mg hydroxychloroquine sulphate tablets.

3. Storage and handling

Hydroxychloroquine sulphate tablets should be stored at room temperature (under 30 degrees C). If supplied by the study then they should be kept in a locked container which is only used for Solidarity protocol drugs. Storage of study drug within a separately locked room is preferable but not essential. Temperature records should be maintained to demonstrate that the tablets were stored appropriately

4. Doses

The tablets can be taken with or without food. There are two loading doses (each of 4 tablets) and 20 maintenance doses (each of 2 tablets). The two loading doses are scheduled to be given 6 hours apart.

The maintenance doses are scheduled to begin 6 hours after the second loading dose and to be given 12 hours apart. Hence, the final maintenance dose is scheduled to be given 10 days after the first loading dose

5. Disposition of unused product

Records of doses dispensed should be kept and provided to study staff on request. If any unopened study-supplied packages of the drug remain when the local lead clinician informs the local lead pharmacist that the study has ended, the pharmacist will inform the lead clinician what supplies remain. The local lead clinician will then decide

on their disposition. Unless there are good reasons otherwise, opened but partially unused packages of study-supplied drug should be destroyed at the end of the study, with proper accountability shared between the local lead pharmacist and the local lead clinician for all study-supplied drug ever received.

6. Maintenance of inventory logs

Use of study-supplied drug should be tracked and recorded on drug disposition logs in case they are required later (as, for example, during post-trial drug accountability checks for the study). Records of when study-supplied doses were dispensed or study-supplied product was destroyed should be kept in these logs.

7. Emergency contact

In the event of an emergency or the need for immediate information regarding product preparation, handling, storage or administration, the local study pharmacist and the local lead clinician should consult together. This product has been in wide use for many years for other indications, so there is extensive experience with it.

SOP-8 Reporting of main outcomes while patient is in hospital

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

At discharge or death, the study doctor will log into WHO website 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.

Patient information will be encrypted and held securely by the WHO. Those analysing it will use only anonymised data, and no identifiable patient details

SOP-9 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARS)

The designated study doctors will access via the study website: **www.who.int/COVIDcore**

The investigator must report any serious adverse events occurring during the clinical trial, even if they are not necessarily in a direct causal relationship with the treatment, to the country sponsor within 24 hours.

All SUSARs (suspected unexpected serious adverse reactions) occurring during a clinical trial at a trial centre must be reported by the Sponsor to the Global Data Safety Monitoring Board, the appropriate National Regulatory Agency and local Ethics Review Committee by the Sponsor within 24 hours (for fatal or life-threatening SUSARs) or 15 days (for all other SUSARs) or in faster timelines if required by local regulations.

This timeframe is from the time when the sponsor receives the SUSAR report. Periodic global safety reports will be developed and shared with all NRAs and ERCs.

If significant new information on an already reported SUSAR is received by the Sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days.

Appendix-1 Global Data Monitoring and Safety Committee

The specific terms of reference of the Global DMSC will be defined during the first meeting. However, as indicated in the protocol, the

A global Data and Safety Monitoring Committee will keep the accumulating drug safety results and major outcome results under regular review. Interim trial analyses are monitored by a Global Data and Safety Monitoring Committee

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 Monitoring and Safety 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.

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 WHO policy-making committee if at any stage the results are sufficiently robust for general release and for affecting global recommendations.

The global Data and Safety Monitoring Committee will keep the accumulating drug safety results under regular review. Suspected unexpected serious adverse reactions that are life-threatening (eg, Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia, or anything comparably uncommon) must be reported within 24 hours of being diagnosed, without waiting for death or discharge.

The WHO may decide to add novel treatment arms while the trial is in progress. Conversely, 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.

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.

Appendix-2 Solidarity trial governance

To be added

Appendix- 3 Protocol amendment history

Version	Date	Description of Change	Brief Rationale