



SOLIDARITY TRIAL PLUS

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**

PROTOCOL

**Version 1.0
April 5, 2021**

This protocol is confidential to trial investigators. It should not be disclosed to others without permission from the WHO, except to seek the consent of collaborators or participants.



Protocol signature page

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

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Contents

Summary	4
Objectives	6
Study population: inclusion, exclusion, and recruitment.....	6
Study products and study drug regimens.....	6
<i>Drug formulation, stability, labelling, preparation, handling, storage and accountability.....</i>	6
Drug discontinuation (which does not imply withdrawal from follow-up).....	7
Decision by a patient or legal representative to withdraw from follow-up	7
Randomization.....	7
Adverse reaction reporting	8
Statistical analyses	8
Study assessments and procedures	9
Sample size.....	10
Drug-specific contraindications	10
<i>Artesunate.....</i>	10
<i>Imatinib</i>	10
<i>Infliximab.....</i>	10
Regulatory, ethical, and study oversight considerations	11
<i>Informed Consent Process</i>	11
<i>Confidentiality and Privacy</i>	11
Key roles and study governance.....	12
<i>Monitoring protocol compliance</i>	12
<i>Source records and study record retention</i>	12
<i>Protocol deviations and violations</i>	13
Sponsorship, and management of conflicts of interest.....	13
Data sharing.....	13
Publications	13
Insurance	13
Statistical Appendix.....	14



Summary

Background: WHO helps evaluate drugs by randomising their effects on important outcomes. The WHO Solidarity trial involves collaboration between hundreds of hospitals in dozens of countries. It began by evaluating four repurposed drugs, and now guided by an independent Expert Groups, is now evaluating addition to the local Standard of Care of other potential drugs.

Simplicity of procedures: Within each country, the national co-ordinator invites selected hospitals and helps them get ethical and regulatory approval and study drugs, then patient recruitment can begin. To facilitate collaboration even in overloaded hospitals, patient enrolment and randomisation (via a cloud-based GCP-compliant platform) and all other trial procedures are greatly simplified, and no paperwork is required. Once consent has been obtained, electronic entry of anonymised details of a few key characteristics of each patient takes only a few minutes. At the end of patient entry, a random treatment allocation is generated.

Eligibility: Adults (age ≥ 18 years), hospitalised with laboratory-confirmed COVID, not expecting transfer within 72 hours, and, in the view of their doctors, with no contra-indication to any potentially relevant study drug.

Consent: The study website <https://data.castoredc.com/studies> has printable patient information in some UN official languages. Once the information has been explained to patients, obtaining consent takes only a few minutes. An electronic image of the signature page is kept (or, if national regulations forbid this, a note to file), and the printed information and original consent stays with the patient or legal representative.

Data collected electronically immediately before randomisation:

- Country, hospital (from a list of approved hospitals) and randomising doctor
- Confirmation that informed consent was obtained from the patient (or a surrogate/ representative)
Age, sex and (yes/no): smoking, *diabetes*, *heart disease*, *chronic liver disease*, chronic lung disease, asthma, HIV, obesity
- Date of onset of symptoms, date of hospitalization, and (yes/no) current/planned use of a few drugs
- Respiratory support (highest level currently being given): A. No oxygen, B. Low-flow oxygen, C. High-flow nasal oxygen, D. Non-invasive ventilation, E. Invasive ventilation, F. ECMO
- SpO₂ (%) and, if not ventilated, respiratory rate
- Any major bilateral lung abnormality? (not imaged/no major abnormality/infiltrations/patchy shadowing)
- Which relevant study drugs are locally available? (yes/no: artesunate, infliximab, imatinib; confirm that none of these locally available drug(s) is, in the doctor's view, definitely contra-indicated)

Trial entry; randomization: Once electronic data collection has been completed the patient automatically enters the trial and a random allocation of their trial treatment is generated (by an algorithm that ensures eventual balance in the characteristics just recorded between each study drug and its controls) and displayed. The patients will be randomly allocated either to Standard of Care (SoC) or to one of the study drugs.

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 decides that deviation from the randomly allocated treatment is appropriate for a particular patient, this should be done, regardless of the random allocation. That patient would still be part of the trial, regardless of what treatment they were actually given.



Safety: Any suspected unexpected serious adverse reactions (SUSARs) that are life-threatening must be reported within 24 hours, as must any other possibly related treatment-related serious adverse events (SAEs). Other adverse events do not need to be reported.

Follow-up: When patients die or are discharged, follow-up ceases and their outcome is reported, regardless of whether the trial treatment actually got given. The following information is to be entered:

- Which study drug(s) got given (and for how long)
- Which of a few selected other drugs were given (and for how long)
- What respiratory support was given (and first and last dates): A No respiratory support, B Low-flow oxygen, C High-flow nasal oxygen, D Non-invasive ventilation, E Invasive ventilation, F ECMO
- Date discharged alive or date of death in hospital and cause of death.
- Pregnant? Yes/No/unknown

Primary and secondary analyses: Primary analyses: In-hospital mortality in all patients. Major secondary analyses: In-hospital mortality subdivided by initial respiratory support. Further secondary analyses: duration of hospital stay in lower-risk patients (A-B); and in higher-risk patients (C-F); and initiation of ventilation in lower-risk patients. The main safety analyses will be of reported SAEs possibly related to the treatment and SUSARs.

Numbers entered: The larger the numbers entered the more accurate the results will be. If substantial numbers get hospitalised in the participating centres, it may be possible to enter several thousand hospitalised patients receiving no oxygen or low-flow supplemental oxygen, and a few thousand receiving high-flow nasal oxygen, ventilation or ECMO, but realistic, appropriate sample sizes will not be estimated at the start of the trial; the numbers that can be entered will depend on the evolution of the epidemic.

Heterogeneity: If a study treatment affects outcome, then this effect could well differ between patients who were receiving different levels of respiratory support when randomised, and separate consideration of these is a secondary analysis. Effects could also differ between younger and older patients, or between patients in one or another country or geographic region. If sufficient numbers are randomised, it may be possible to obtain statistically reliable treatment comparisons within each of several different countries/regions or types of patient.

Adaptive design: A global Data and Safety Monitoring Committee will keep the accumulating safety results and major outcome results under regular review. The WHO may recommend adding further treatment arms while the trial is in progress, if evidence emerges that there are suitable candidate therapeutics. 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 or other of the trial treatments definitely does or does not affect 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 of trial patients (perhaps through linkage to electronic healthcare records and routine medical databases). These could be thought of as Phase 2b trials that are being conducted concurrently with the Phase 3 trial. However, while well-organised additional research studies of the natural history of the disease or 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. Major findings will be disseminated by the WHO and published in the names of the collaborators.



Objectives

The primary outcome is in-hospital mortality from any cause, and the primary analyses are of mortality in all randomised patients. The major secondary outcomes are initiation of ventilation, and duration of hospital stay.

The main safety analyses will be of reported SAEs and SUSARs possibly related to the treatment and SUSARs. Numbers of deaths in hospital attributed to causes other than COVID-19 will also be reported.

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, 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

The only patients invited will be those admitted to a collaborating hospital; no wider recruitment is expected.

Eligibility (see SOPs 1 to 3 for additional details):

- adults (age ≥ 18 years, which allows consent),
- recently hospitalised (or already in hospital) with laboratory-confirmed COVID,
- not expected to be transferred within 72 hours,
- with, in the view of their doctors, no contra-indication to any potentially relevant study drug.

Study products and study drug regimens

These are described in SOPs 4 to 6.

- Artesunate: 2.4 mg/kg/dose at 0 hours, 12 hours, and 24 hours and thereafter every 24 hours; IV injection; duration of treatment 7 days. This is the standard dose recommended for the treatment of severe malaria.
- Infliximab: 5 mg/kg/dose (once only), single IV infusion over 2 hours. This is the standard dose that is given repeatedly for the treatment of psoriasis.
- Imatinib: 400 mg/dose; orally once daily; duration of treatment 14 days. This is the standard maintenance dose which is at the lower end of that used for several years in the treatment of hematological malignancies.

Drug formulation, stability, labelling, preparation, handling, storage and accountability

Study drugs will be shipped to participating hospitals from regional or local drug repositories. All other supplies will be provided by the participating hospital. The participating hospital's principal investigator is responsible for study drug disposition and accountability. SOPs 4 to 6 give details of each study product.



Drug discontinuation (which does not imply withdrawal from follow-up)

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 any deviation from the randomly allocated treatment arm is definitely appropriate then this should be done, although the patient would remain in the trial and should still be reported on.

1. Study drug administration should be stopped if the team suspects any serious unexpected drug-related adverse reaction that is life-threatening, and this SUSAR should immediately be reported electronically. The patient will still be reported on in the usual way at the end of their time in hospital.
2. Study drug administration should be stopped if the treating physician considers this is definitely in the patients' best interest (including but not limited to life threatening events) or if the patient or a legal representative decide it should be stopped. The patient should still be reported on in the usual way at the end of their time in hospital, unless it is decided otherwise (see below).

Decision by a patient or legal representative to withdraw from follow-up

Patients are informed at study entry of their right to withdraw at any time their consent to participate without any adverse consequence and without giving any reason. Withdrawal from the treatment that was randomly allocated at study entry need not imply withdrawal from information on outcome in hospital being reported to the WHO at the end of the hospital stay. But, if the patient (or a legal representative) decides the patient will withdraw *and* that no further data will be sent to the WHO study office, then only the date of withdrawal will be reported; no further information will be given, unless an adverse drug reaction report is legally required.

Randomization

In addition to receiving usual care, eligible patients will be randomized using a central web-based service. Patients will be randomized between Standard of Care and other treatment options.

As the patient is being entered into the trial, neither the patient nor the physician knows which treatment will be allocated after data entry is complete. Hence, foreknowledge of the treatment that would be randomly allocated if patient entry takes place cannot bias the decision to enter the study and cannot affect the electronic data collection immediately before randomization.

Random allocation takes place automatically as soon as the electronic data entry has been completed. The patient is then in the trial (and remains in it whatever treatment is given, unless the patient decides otherwise: see SOP-2). This is an open-label study. However, while the study is in progress access to tabular results of study outcomes by allocated treatment allocation will not be available to the research team, patients, or members of the Trial Executive Group (unless the DSMC advises otherwise).



Adverse reaction reporting

Any suspected unexpected serious adverse reactions (SUSARs) that are life-threatening must be reported electronically within 24 hours of diagnosis, without waiting for death or discharge; see SOP-8, as must any other potentially treatment-related serious adverse events (SAEs). Other adverse events do not need to be reported. A subset of countries or collaborators will also collect fuller information on adverse events. Where countries collect more extensive adverse reaction data, those datasets are not included in the Solidarity trial dataset.

In addition to reporting SAEs possibly related to the treatment and SUSARs, doctors will be asked, after patient discharge or death in hospital, what was the probable cause of death, and will be asked about drug use and respiratory support in hospital, including initiation of ventilation. Information on other non-fatal adverse outcomes is not in general required. It is, however, anticipated that some centres will choose to collect more detailed information on adverse events (eg, through linkage to medical databases) or on other aspects of outcome (eg, laboratory or radiological features), but this is not a requirement of the core protocol.

Statistical analyses

All analyses relate outcome to the randomly allocated treatment. (These are called “intent-to-treat” analyses.) The controls for those randomly allocated one particular study drug will be those patients who could (at the time and place they entered the study) have been randomly allocated that study drug, but instead got allocated to the local Standard of Care without any of the study drugs. The comparison between a study drug and its control group is evenly randomized (1:1). It is also unbiased, as those allocated a study drug and those allocated its control are, but for the play of chance at randomization, affected equally by any differences between countries or hospitals and by any time trends in patient characteristics or standard of care.

The primary analysis will assess any effects of treatment allocation on all-cause in-hospital mortality in all patients. The main secondary analyses will assess in-hospital mortality subdivided by initial respiratory support. Further secondary analyses will assess initiation of ventilation in lower-risk patients, and, separately, duration of hospital stay in lower-risk patients (A-B) and in higher-risk patients (C-F).

If there are real effects of treatment, their magnitude might depend on many factors (eg, age), so additional subgroup analyses will also be reported, seeking evidence of trends in the treatment-versus-control relative risks, but these additional subgroup analyses will be treated as hypothesis generators rather than hypothesis testers.

Analyses of in-hospital mortality and of time to discharge will use log-rank methods and unstratified Kaplan-Meier graphs, with appropriately defined denominators (see Statistical Appendix). Log-rank analyses yield both death rate ratios, RRs (where $RR < 1$ means active treatment is better) and discharge rate ratios (where the opposite is true; $RR > 1$ means active treatment is better). These analyses also yield confidence intervals and p-values. Kaplan-Meier graphs give cumulative events by days since randomisation. Although these graphs will be plotted only up to day 28, the log-rank analyses and p-values will make full use of all events in hospital both before and after day 28.



Subsidiary analyses will tabulate treatment allocation versus reported numbers of SUSARs and SAEs possibly related to the treatment, but will consider the open-label design in interpreting such tabulations. An early interim safety analysis may be planned as necessary.

Study assessments and procedures

	At study entry	During hospitalization	At death or discharge
ELIGIBILITY			
Adults (age ≥18 years) recently hospitalised or already in hospital with COVID and not expecting transfer within 72 hours, who have, in the view of their doctors, no contra-indication to any potentially relevant study drug (SOP-2)	X		
1. Confirmation of consent entered electronically into https://data.castoredc.com/ but information sheet and documents kept by the patient (SOP-3)	X		
2. Brief patient details (eg, concomitant conditions, level of respiratory support etc) entered electronically into https://data.castoredc.com/ (SOP-2)	X		
RANDOMIZATION			
3. Immediately after all details have been provided, the computer enters the patient into the trial; and generates and displays the patient's ID code and the random treatment allocation (SOP-2)	X		
STUDY INTERVENTION AND SAFETY MONITORING			
4. Administer any study drug specified by the random allocation		X	
5. (SOP 4-6), unless this trial treatment is thought considered contraindicated			
6. Report SUSARs or potentially treatment-related SAEs within 24 hours electronically into https://data.castoredc.com/ (SOP-8)		X	
REPORTING OUTCOMES AFTER DISCHARGE OR DEATH			
Enter into https://data.castoredc.com/ the in-hospital treatment (study drug, respiratory support given, duration of stay) and date and cause of death in hospital or date discharged alive (SOP-2)			X
7. A reminder will sent to the hospital if the patient outcome (or study withdrawal) has not already been reported within 6 weeks of randomisation. If this is because patient has not yet been discharged, this fact is (temporarily) all that needs to be reported .			(Reminder)



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 need to be recruited into the trial to give reliable answers.

The larger the numbers entered the more accurate the results will be, but the numbers that can be entered will depend on how the epidemic evolves. 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 large numbers are randomised, it may be possible to obtain statistically reliable treatment comparisons within each of several different countries or types of patient.

Drug-specific contraindications

Patients with known hypersensitivity to any study drug or its excipients should not be entered into the trial. But, as most patients will have had no relevant exposure, hypersensitivity may be unrecognised before entry. If, at any later time, hypersensitivity is recognised then the study treatment should be withheld, or discontinued, as the local medical team should always act in the patient's best interest.

Artesunate

Hypersensitivity to Artesunate or other artemisinins or to any of the components of the formulation. Delayed haemolytic anaemia is unlikely in the context of COVID, the post-treatment haemolytic anaemia resulting from the destruction of malaria infected red blood cells. However, a follow-up complete blood count approximately 2 weeks after the end of treatment may be considered given the neutropenia reported after receiving high doses.

Imatinib

Hypersensitivity to the active substance or to any of the excipients.
The metabolism of Imatinib is primarily hepatic and special caution should be taken in patients with hepatic dysfunction. There is limited data on its use during pregnancy and breastfeeding. Pregnant women and patients with hepatic disease were excluded from randomisation, as there is limited data on Imatinib use in pregnancy, and hepatic dysfunction impairs Imatinib metabolism. In the context of COVID, the interaction with fentanyl, which results in a significant increase in fentanyl exposure, requires great caution when sedating with fentanyl.

Infliximab

Hypersensitivity to the active substance or to any of the excipients.
Moderate or severe heart failure.
Tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections.



The trial gives Infliximab only once, however, and to further limit any such risks it excludes patients with heart failure, TB or liver disease. Reactivation of latent tuberculosis, as well as that of hepatitis B, in chronic carriers of this virus (HBV), has occurred in patients receiving a TNF antagonist, including infliximab. Even in this single administration setting, screening for latent tuberculosis as well as HBV should be considered whenever possible and appropriate referral to treatment if necessary (local recommendations may apply). Treatment of the study does not have to wait for the results.

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 it cannot be substantially altered or rewritten. Likewise, any substantial amendments made centrally to the core protocol or consent procedure while the trial is in progress can be approved or rejected by local ethics committees but cannot be materially altered or rewritten.

Informed Consent Process

When obtaining informed consent (SOP-3), this must be documented by a signed and dated written consent form. As indicated in the eCRF, an electronic image of the signature page is kept (or a note to file if national regulations forbid this) in the trial platform using a secure GCP-compliant application that immediately encrypts and safely stores the data. Printed information and original consent stays with the patient or legal representative, isolated from study staff.

Methods other than a face-to-face consent interview may be acceptable if they allow for an adequate exchange of information and documentation, and a method to ensure that the signer of the consent form is the person who plans to enrol as a subject in the clinical investigation or is the legally authorized representative of the subject. Only if acceptable in the country, deferred consent will involve randomization at the investigator's discretion according to criteria that have been explicit during national ethical approval of the protocol, followed by the request for patient's (deferred subject consent) or representative's (deferred proxy consent) informed consent in a later phase. There should be a proxy independent party that would determine whether the patient is incapable or lacks capacity to provide deferred informed consent.

If the patient previously declined to consent, then deferred consent is not applicable and will not be pursued. Extemporized oral translations/interpretations of the consent form will be avoided. Where deferred consent is not acceptable, patients unable to give consent and without a surrogate will not be included in the study.

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 during study analysis, when study results are disseminated, and afterwards.



Key roles and study governance

Interim trial analyses will be monitored by a Global Data and Safety Monitoring Committee (Appendix 1). Otherwise, the WHO, collaborators, and administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results. The trial governance is described in Appendix 2.

The Global Data and Safety Monitoring Committee will independently evaluate the interim analyses and will inform the Executive Group of the Steering Committee if at any stage the results are, in their judgement, sufficiently robust for general release (ie, strong enough and with a sufficiently narrow range of uncertainty around the findings to affect national and global treatment strategies).

Monitoring protocol compliance

Monitoring to ensure trial patients are protected and the trial data are timely and complete will be conducted mainly by central data checks, not by site visits (which are avoided, partly to limit the spread of infection and partly because central checks may well be better at detecting possible problems). In addition, every country will identify local monitors to help local site staff resolve any problems, and to provide training focussed on any specific local needs. Monitoring will be implemented in compliance with international regulations. The Clinical Trial Unit of the University of Bern will conduct the global monitoring. Their SOPs state that the focus of this will be on those factors that are critical to quality (ie, to patient safety and the reliability of the trial findings). Remedial actions would therefore focus on issues with the potential to have a material impact on these issues.

Clinical data monitoring

This will include electronic completeness checks for all records, although the information recorded initially must have appeared complete at the time for the system to have proceeded to patient entry, ie, to generation of a treatment assignment. Items for which electronic plausibility checks would be possible include:

- Patient characteristics.
- Dates of symptom onset, hospital admission, consent, study entry and exit.
- Drugs and respiratory support: check compatibility of start and stop dates with other information.
- Date and cause of death in hospital or date discharged alive: check compatibility with other information.
- Unduly common discrepancies at a centre between allocated trial treatment and treatment actually given.

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 ends. 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 co-sponsor of the trial. The sponsor and regulatory agencies will have the right to conduct confidential audits of such records (but should be



mindful of the workload facing participating hospitals and the infection control requirements during this pandemic).

Protocol deviations and violations

The study will be conducted in accordance with the principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and relevant local, national and international regulations. Any serious breach of GCP will be handled in accordance with regulatory requirements and classified as protocol deviations or violations.

As the protocol leaves the local doctors 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, This should be reported within 24 hours on the study website. The DSMC chair will then decide whether this constitutes a sufficiently major protocol deviation to be forwarded promptly to the relevant national co-ordinator and 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 Organization. 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](#). Although the writing committee will consist of the executive group and the WHO trial secretariat, authorship will include all steering committee members and local collaborators whose hospital, in the view of the national PI, contributed substantially towards the trial.

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 and stakeholders that participate in the trial.



Statistical Appendix

For all primary and secondary analyses, comparisons will be made between all participants randomised to the relevant treatment arms, irrespective of whether they received their randomly allocated treatment ("intention-to-treat" analyses, excluding any with retrospective consent refused or opt-out from follow-up). Statistical methods will be closely modelled on those used previously (New Engl J Med 2021; 384: 497-511).

Graphs of in-hospital mortality by time will be from unstratified Kaplan-Meier methods, calculated with the denominators that are needed to yield in-hospital mortality (eg, if, of 100 patients, 99 are discharged alive before the last one dies, in-hospital mortality is 1% and at the time of that death the probability of not having died in hospital is multiplied by 99/100; this denominator includes those already discharged).

The risk on Day N will be calculated by first excluding patients with outcome not reported or with study entry less than N days before dataset closure (or transferred elsewhere before Day N); then, the number of in-hospital deaths on Day N is divided by the total number of patients in hospital on Day N or discharged alive before Day N. This denominator (or "risk set"), which includes those discharged before Day N, is also used to calculate the contribution of Day N to the log-rank (and Cox) analyses of in-hospital mortality.

If the log-rank Observed minus Expected number of deaths is $O-E$ with variance V , then $b = \log eRR$ is calculated as $(O-E)/V$ with variance $1/V$ and a Normal distribution. (For, if event times are accurate and $L[b]$ is the Cox log-likelihood, the first and second derivatives of $L[b]$ at $b=0$ are $[O-E]$ and $-V$.)

Forest plots of subgroup-specific results (with 95% CIs only for the primary analysis, otherwise with 99% CIs to allow for subgroup multiplicity) and chi-squared statistics (sum of $[O-E]^2/V$) help interpret any apparent heterogeneity of RRs between subgroups. All RRs describe *proportional* risk reductions; *absolute* risk reductions also depend on background risks, which in future practice might differ from those in the trial.

For the analyses of time to discharge the methods will be broadly similar except that only 99% confidence limits will be cited. Also, the denominators needed for analyses of discharge rates on day N differ from those for analyses of mortality on day N, as death in hospital means that discharge will never happen.

So, although log-rank methods and Kaplan-Meier methods will again be used, the denominators that are used for any log-rank analyses, Cox analyses or Kaplan-Meier analyses of the discharge rate on day N will *exclude* those already discharged but *include* those already dead. Analyses will use SASv9.4 and Rv4.02.

[Ends]