

CRASH-19

STUDY PROTOCOL

(INTERNATIONAL PROTOCOL)

FULL TITLE	Aspirin, losartan and simvastatin in hospitalised COVID-19 patients: a multinational randomised open-label factorial trial
SHORT TITLE	Coronavirus Response - Active Support for Hospitalised COVID-19 patients
ACRONYM	CRASH-19

Clinicaltrials.gov Number:	NCT04343001
Sponsor ID Number	2020-KEP-420

	NUMBER	DATE	Description
VERSION	1.0	23 April 2020	Final Version

Contents

1.	BACKGROUND AND RATIONALE.....	5
2.	TRIAL DESIGN AND PROCEDURES.....	9
2.1.	Design concept.....	9
2.2.	Setting.....	9
2.3.	Eligibility and consent.....	10
2.4.	Baseline data.....	11
2.5.	Randomisation and allocation concealment.....	11
2.6.	Follow-up data.....	11
2.7.	Withdrawal criteria.....	12
2.8.	End of trial.....	12
3.	PHARMACOVIGILANCE.....	13
3.1.	Adverse events.....	13
3.2.	Data Monitoring Committee.....	13
3.3.	Trial Steering Committee.....	14
4.	DATA ANALYSIS AND MANAGEMENT.....	14
4.1.	Sample size.....	14
4.2.	Statistics and Data analysis.....	15
4.3.	Data management.....	15
5.	ETHICAL, REGULATORY AND OPERATIONAL CONSIDERATIONS.....	15
5.1.	Research Ethics Committee review.....	15
5.2.	Monitoring, audit and inspection.....	16
5.3.	Trial sponsor and coordination.....	17
5.4.	Indemnity.....	17
5.5.	Supply of trial treatments.....	17
5.6.	Funding.....	18
5.7.	Dissemination.....	18
6.	REFERENCES.....	19
7.	APPENDICES.....	21
	Appendix 1: Contraindications to trial treatments.....	21
	Appendix 2: Entry form.....	22
	Appendix 3: Outcome form.....	23
	Appendix 4: Information sheet and consent form.....	24
	Appendix 5: Trial organisation and responsibilities.....	29
	Appendix 6: Protocol change log.....	32
	Appendix 7: Guidance on professional legal representatives.....	33

PROTOCOL SUMMARY

Background: Patients with COVID-19 infection typically present with fever, muscle aches and a dry cough. Although most have a mild illness, older people and those with chronic health problems, particularly cardiovascular disease, can develop a severe viral pneumonia with a poor prognosis. Cardiac complications, in particular myocardial infarction and heart failure are common in viral pneumonia and the high troponin levels in COVID-19 non-survivors strongly suggest that cardiac events are an important cause of death. A cohort study of 416 patients admitted to hospital in Wuhan with COVID-19 found that cardiac injury, defined as high sensitivity troponin 1 levels >99% upper reference limit, was seen in 20% of patients. These patients were more likely to receive mechanical ventilation (22.0% vs 4.2%; $P < 0.001$) and were more likely to die (51.2% vs 4.5%; $P < 0.001$). Acute respiratory distress syndrome (ARDS) is a clinical syndrome often seen in patients with viral pneumonia and is particularly common in severe COVID-19 infection.

The incubation period (time from infection to first symptoms) for COVID-19 is about 5 days. The time from symptom onset to hospital admission is about 6 days. By the time patients are admitted they have been infected with the virus for over 10 days and have an established viral pneumonia. At the time of protocol development, there were no approved anti-viral treatments for COVID-19. Although trials have started, supportive care is the mainstay of management. Optimising the effectiveness of supportive care is therefore of utmost importance and is the objective of this trial.

Aim: The CRASH-19 trial will assess the effectiveness and safety of supportive care interventions for patients hospitalised with suspected or confirmed acute COVID-19 infection with a focus on cardiac and pulmonary protection. We will evaluate the effects of aspirin, the angiotensin receptor blocker losartan, and simvastatin compared with standard care. If during the course of the trial there are changes in routine care as a consequence of new information, patients receiving this new routine care would be still be eligible for recruitment (unless it includes any of the treatments being evaluated in this trial).

Trial design: The CRASH-19 trial is a multinational, open-label, factorial, randomised trial in adults hospitalised with suspected or confirmed acute COVID-19 infection. The design is pragmatic and efficient to allow rapid recruitment while minimising the burden on front-line health workers. Eligibility criteria and consent procedures are practical in the emergency setting. The open-label design avoids the need for trial specific drug manufacture and shipping to participating hospitals. Recruiting clinicians can access the randomisation service on-line that will provide the allocated treatment which is then prescribed and administered. Only essential data are collected with follow-up data based on medical records.

Setting: This trial is coordinated from the London School of Hygiene & Tropical Medicine (University of London) and will be conducted in an established network of hospitals internationally.

Eligibility criteria: Adults with suspected or confirmed acute COVID-19 infection (fever and at least one symptom of respiratory disease requiring hospitalisation) who are ≥ 40 years old are potentially eligible. Pregnant women and patients already receiving, or with a definite indication or contraindication for any of the trial treatments, are excluded. People who are already on mechanical ventilation via an endotracheal tube, very severely frail (completely dependent and approaching end of life who typically could not recover even from a mild illness) or terminally ill should not be recruited.

Sample size: Because of the scale of the COVID-19 pandemic, there is no shortage of potentially eligible patients and even moderate treatment benefits could potentially avert many thousands of premature deaths. Assuming a baseline case fatality of 15%, a trial with about 10,000 patients would have over 90% power to detect a reduction from 15% to 12% (RR=0.8) at the 0.01 level of significance.

Procedures: We will evaluate the effect of aspirin (150mg once daily), losartan (100mg once daily), and simvastatin (80mg once daily) in patients with suspected or confirmed COVID-19 infection. Eligible patients will be randomly allocated to one of eight arms (aspirin only; losartan only; simvastatin only; aspirin and losartan; aspirin and simvastatin; losartan and simvastatin; aspirin, losartan and simvastatin; standard care only). Trial treatments are given in addition to the usual standard of care at the trial hospital. The dose of Losartan may be reduced to 50 mg or stopped in instances where the clinician is concerned about severe hypotension and restarted at anytime up to the end of the treatment period. An independent Data Monitoring Committee (DMC) will monitor interim analyses and assess whether any of the randomised comparisons provide sufficiently strong evidence, with adequate precision of the treatment effect, to inform international treatment recommendations. In such circumstances, the results will be disseminated, and the arms adjusted as necessary.

Duration of treatment and participation: Treatment will be started as soon as possible after randomisation and will continue until follow-up which is at death, discharge or 28 days after randomisation, whichever occurs first.

Outcomes: The primary outcome is in-hospital death (cause of death will be recorded). Secondary outcomes are myocardial infarction, cardiac failure, severe cardiac arrhythmia, myocarditis, respiratory failure including ARDS, viral pneumonitis, acute renal failure, sepsis, stroke, gastrointestinal bleeding, receipt of non-invasive or mechanical ventilation requiring endotracheal intubation, ability to self-care at hospital discharge and time to hospital discharge.

1. BACKGROUND AND RATIONALE

Effective supportive care is essential in patients with COVID-19 infection

Most patients hospitalised with COVID-19 infection have been exposed to the virus for about 10 days and have severe viral pneumonia. At the time of writing, there are no approved anti-viral treatments for COVID-19. Although trials have started, supportive care is the mainstay of COVID-19 management. Optimising the effectiveness of supportive care is therefore of utmost importance and is the objective of the CRASH-19 trial. The global health importance of supportive care was shown clearly in the 2014–16 West African Ebola epidemic. Without any anti-viral treatments, fatality fell from over 70% to under 40%, mainly due to improvements in supportive care.

Cardiac effects of COVID-19 infection

Cardiac injury is common in patients with COVID-19 infection and increases the risk of respiratory failure and death.¹ A cohort study of 416 patients admitted to hospital in Wuhan with COVID-19 found that cardiac injury, defined as high sensitivity troponin 1 levels >99% upper reference limit, was seen in 20% of patients.² These patients were more likely to receive mechanical ventilation (22.0% vs 4.2%; $P < .001$) and were more likely to die (51.2% vs 4.5%; $P < .001$). The association between cardiac injury and mortality remained after adjusting for age and co-morbidity (HR 4.26, 95% CI, 1.92-9.49). The risk of death increased steeply with increasing cardiac troponin levels. Although electrocardiograms (ECG) were available for only 27% of patients, abnormalities were seen in two thirds with ECG findings indicative of myocardial ischemia, such T-wave depression and inversion, ST-segment depression, and Q waves. In a single centre case series of 187 COVID-19 patients in China, the mortality rate was much higher among 28% of patients with elevated cardiac troponin levels (60% vs 9%).³ These results are consistent with previous reports showing that COVID-19 infected patients with raised inflammatory markers (IL6), activated coagulation (raised d-dimer levels) and high cardiac troponin levels had a higher mortality.^{4–7} The first autopsy of a 53-year-old woman who died after COVID-19 infection in Wuhan showed acute myocardial infarction.⁸

The strong association between acute respiratory infections and myocardial infarction is well documented.^{1,9–11} Several self-controlled case series have shown that acute respiratory infections, including those due to coronaviruses, are associated with a transient but greatly increased risk of vascular occlusive events. In the first 3 days after seeking medical care for a viral respiratory infection, the risk of myocardial infarction is increased fourfold (incidence ratio 4.95; 95%CI 4.43 to 5.53) and remains raised for about one month.¹⁰ Systemic inflammation due to viral infection has haemostatic effects (increased platelet aggregation, raised fibrinogen, increased plasma viscosity) and haemodynamic effects (increased metabolic demand, coronary vasoconstriction, hypoxaemia). A study in healthy volunteers used vaccination to provoke

a mild inflammatory response and found a temporary but profound disturbance in vascular tone.¹² Localised inflammation within atherosclerotic plaques may precipitate rupture and thrombosis.^{13,14}

Worsening heart failure is also common in viral pneumonia. The mechanisms through which infection worsens heart failure are uncertain but it may be the result of raised metabolic demand and increased sympathetic activity. However, COVID-19 infection may have a more specific effect. Angiotensin receptors appear to play a central role in COVID-19 infection. The spike protein of the virus binds to ACE2 receptors in the lung and this is believed to be the way in which the virus enters into lung cells. The binding of virus to ACE2 receptors leads to their down-regulation. Because ACE2 degrades angiotensin 2 (a potent vasoconstrictor), ACE2 down-regulation may lead to increased levels of vasoconstricting, pro-inflammatory angiotensin 2. In animal models of lung injury, ACE2 is protective. Elevated angiotensin 2 levels may worsen heart failure and lung injury in COVID-19 infection.

Acute respiratory distress syndrome in COVID-19 infection

Acute respiratory distress syndrome (ARDS) is a clinical syndrome often seen in patients with viral pneumonia and is particularly common in severe COVID-19 infection.¹⁵ A cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to hospital in Wuhan found that 42% developed ARDS, half of whom died.⁵ In a second Wuhan study of 150 confirmed cases, ARDS occurred in 81% of non-survivors compared with 9% of survivors.⁶ Mechanical ventilation and supportive care are the mainstay of ARDS management and randomised trials of ventilation and fluid management strategies have improved outcomes.¹⁵ Currently there are no effective pharmacological treatments although some have shown promise in pre-clinical studies and early phase trials.

Protecting the heart and lungs to reduce mortality

With over 1.2 million confirmed cases of COVID-19 infection and almost 70,000 deaths globally as of April 6 2020, an effective treatment is needed urgently. Outbreaks in many countries are spreading, and the situation will be particularly bleak in low- and middle-income countries. Epidemiological models show that the number of patients that will need mechanical ventilation for COVID-19 induced ARDS could greatly exceed supply. Even a modest reduction in mortality from an inexpensive and widely practicable treatment that adds little additional burden to hospital staff working in overstretched health systems would be helpful. Treatments that confer cardiac or pulmonary protection have the potential to benefit COVID-19 patients.¹⁶

Aspirin (anti-platelet): Aspirin is an antiplatelet agent that reduces serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in patients with occlusive vascular disease. Aspirin inhibits platelet aggregation through the irreversible acetylation of cyclooxygenase 1 with reduced

thromboxane A2 production. The net benefit of aspirin is less certain in patients without vascular disease because the reduction in vascular occlusive events must be balanced against the increased risk of bleeding. However, because patients with COVID-19 infection have greatly increased risks of myocardial infarction, the balance of risks and benefits should be favourable. Platelet activation is also implicated in the pathogenesis of acute lung injury and aspirin may have a role in preventing ARDS. The Lung Injury Prevention with Aspirin (LIPS-A) trial evaluated the effect of pre-treatment with aspirin (325-mg loading dose followed by 81mg per day) on the risk of ARDS in 400 high risk adults. Although there was no significant reduction in ARDS or 28-day mortality in this early phase study, the trial was not large enough to confirm or refute a modest benefit and larger trials are needed. Aspirin is inexpensive and widely available. We will evaluate the effect of once daily aspirin (150mg) in patients with acute COVID-19 infection.

Losartan (Angiotensin II Receptor Blocker): Losartan is an angiotensin II receptor blocker (ARB) used to treat high blood pressure and heart failure. By blocking the angiotensin II receptor (AT1R), losartan might reduce cardiovascular strain from excessive vasoconstriction in patients with COVID-19 infection (see *Figure 1*). It might also reduce lung damage by reducing pulmonary vascular permeability.¹⁷ Although data from animal studies showing that ARBs can up-regulate ACE2 expression have caused speculation that this might increase COVID-19 susceptibility, there is no experimental or clinical evidence to support this claim and authorities advise that people taking losartan for blood pressure control should continue to do so.^{18,19} Indeed, it may be harmful to withdraw treatment in high-risk COVID-19 patients. Following the down-regulation of ACE2 by SARS-CoV-2, up-regulation by ARBs may counteract excessive angiotensin II (AT2) production and increase angiotensin 1-7 (AT1-7) production.²⁰ Losartan is widely used, well tolerated and has an established safety profile. Because ARBs affect foetal blood pressure, pregnant women are excluded.

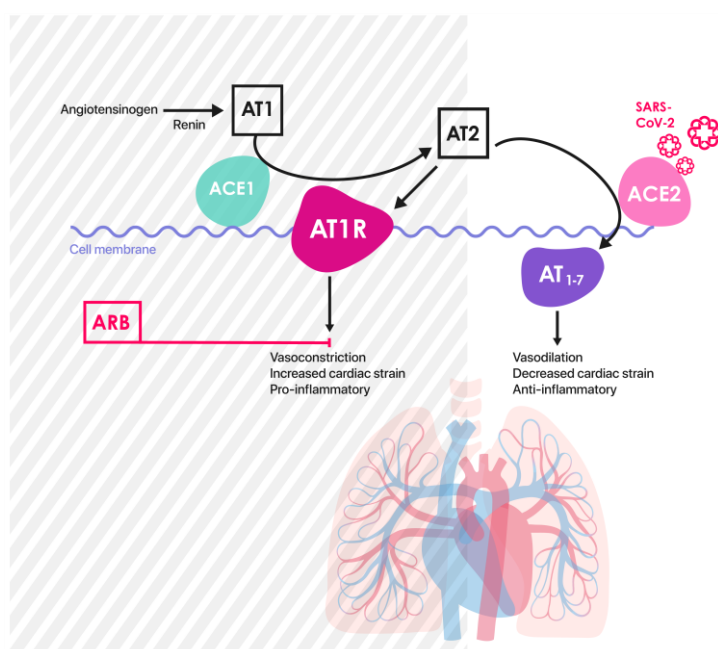


Figure 1. The Renin Angiotensin Aldosterone System (RAAS): Angiotensin converting enzyme 1 (ACE1) converts angiotensin 1 (AT1) into angiotensin II (AT2). Angiotensin converting enzyme 2 (ACE2), a functional receptor for SARS-CoV-2, inactivates AT2 by cleaving it into angiotensin 1-7 (AT1-7). AT1-7 stimulates vasodilation, decreases cardiac output and has anti-inflammatory effects. AT2 binds to

angiotensin II type I receptors (AT1R), increasing vasoconstriction, cardiac output and inflammation. By binding to AT1R, angiotensin II receptor blockers (ARBs) inhibit the action of AT2, helping to lower blood pressure and reduce cardiac strain.

We will evaluate the effect of once daily losartan (100 mg) in patients with acute COVID-19 infection. The dose of Losartan may be reduced to 50 mg or stopped in instances where the clinician is concerned about severe hypotension and restarted at anytime up to the end of the treatment period.

Simvastatin (Hydroxymethylglutaryl-CoA reductase inhibitor): Statins lower cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. In addition to their well-established benefits in ischaemic heart disease, statins modify some of the biological mechanisms in the pathophysiology of ARDS. Statins reduced lung inflammation and lung injury in animal models of ARDS and simvastatin has been shown to reduce lung inflammation in a human ARDS model induced by lipopolysaccharide inhalation.^{21,22} Cohort studies and meta-analyses of randomised trials show that statins are safe in critical illness and may improve survival.²³ The HARP-2 trial randomly allocated 540 ARDS patients to receive simvastatin (80mg) or placebo once daily for up to 28 days. Although there were fewer deaths in statin treated patients (22% versus 27%) this reduction is compatible with the play of chance (RR=0.8 95%CI 0.6 to 1.1).²⁴ ARDS is the leading cause of death in patients with COVID-19 infection. ARDS is a heterogeneous disease with distinct phenotypes. About 35% of patients have hyper-inflammatory ARDS characterised by raised inflammatory markers (e.g. IL-6), profound shock and high mortality. The remaining 65% have hypo-inflammatory ARDS with a much lower mortality. Secondary analyses of data from the HARP-2 trial, stratified by ARDS phenotype show that in hyper-inflammatory ARDS, there was a significantly higher 28-day survival ($p = 0.008$) in simvastatin (68%) treated compared with placebo (55%).²⁵ Comparisons of IL6 levels in survivors and non-survivors show greatly elevated IL6 levels in non-survivors, strongly suggesting a hyper-inflammatory ARDS phenotype. Simvastatin is widely used to lower cholesterol, is well tolerated and has an established safety profile. We will evaluate the effect of once daily simvastatin (80mg) in patients with acute COVID-19 infection.

2. TRIAL DESIGN AND PROCEDURES

2.1. Design concept

Previous CRASH trials were international multi-centre trials conducted in high-pressure emergency settings.^{26,27} The CRASH-19 trial uses the same design principles but even more streamlined procedures to allow rapid recruitment whilst minimising the burden on health care workers in this pandemic. Eligibility criteria and consent procedures are simple and practical and well tested in emergency settings. The open-label design avoids the need for the manufacture and shipping of trial specific drugs to participating hospitals. Healthcare professionals can access a rapid randomisation service via the internet that will give the allocated treatment which is then prescribed and administered. We collect only key baseline and follow-up data using brief data collection forms. Follow-up data are obtained from the routinely collected information in patients' medical records with no extra tests. Short-term follow-up ensures complete outcome data (previous CRASH trials achieved over 98% follow-up), minimising loss of study power and the risk of bias.

We use a 2 x 2 x 2 factorial design because it allows us to evaluate several different treatments in the same trial. Although the factorial design may seem complicated, appropriate analysis of this design means that all participants contribute to the assessment of the separate effects of each treatment and at the same time providing information on their combined effects. Apart from the allocated treatments, all other aspects of participant care are at the discretion of the responsible health care professionals. Participants will receive the allocated treatment daily until the end of follow-up or if the responsible clinician decides to cease treatment. The treatment arms are as follows:

Arm 1: Aspirin 150 mg once daily

Arm 2: Losartan 100 mg once daily

Arm 3: Simvastatin 80 mg once daily

Arm 4: Aspirin 150 mg and Losartan 100 mg once daily

Arm 5: Aspirin 150 mg once daily and Simvastatin 80 mg once daily

Arm 6: Losartan 100 mg once daily and Simvastatin 80 mg once daily

Arm 7: Aspirin 150 mg, Losartan 100 mg and Simvastatin 80 mg once daily

Arm 8: Standard care control (no additional treatment)

2.2. Setting

The trial will be conducted in hospitals worldwide. Co-enrolment into other clinical trials is encouraged where the interventions do not have a similar biological effect to those being studied in CRASH-19.

2.3. Eligibility and consent

Potentially eligible participants will be identified by treating clinicians. Adults admitted to hospital with suspected or confirmed acute COVID-19 infection who are believed to be ≥ 40 years old are eligible.

We use the following WHO criteria for a suspected case:

A. A patient with acute respiratory illness (fever and at least one sign or symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Patients hospitalised without symptoms of acute COVID-19 infection should not be recruited even if they test positive for COVID-19. Women known to be pregnant and patients already receiving, or with a definite indication or contraindication for any of the trial treatments are excluded. People who are already on mechanical ventilation (i.e. with an endotracheal tube in situ), who are very severely frail (completely dependent and approaching end of life who typically could not recover even from a mild illness) or terminally ill should not be recruited. We are limiting recruitment to patients aged ≥ 40 years because the risk of death from COVID-19 infection is higher at older ages, partly due to underlying comorbidities.

For patients who fulfil the eligibility criteria and who are competent at the time of recruitment, we will provide information about the trial and seek their written consent to take part. However, many potential participants will be seriously ill and unable to provide written informed consent. If a relative is present, we will provide information about the trial and seek consent to take part. If the relatives object, the patient will not be recruited. In the case of COVID-19 infection, relatives who might normally be able to act as personal representatives might be unavailable due to isolation or lockdown measures and even if available, their ability to give informed consent might be limited in this high stress situation. If the personal representative is not immediately available or unable to provide consent, randomisation will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the professional legal representative. Consent will then be obtained from the patient's personal representative (or directly from the patient if they recover) at the earliest opportunity for ongoing trial procedures. Where a patient dies before consent is obtained, it will be the treating clinician's decision as to whether relatives can be approached to obtain consent.

As there is a potential risk of cross-infection by removing paper documents from the clinical area for secure storage, at sites where the risk of cross infection is high, an electronic image of the consent form will be retained and transmitted as an encrypted document to London School of Hygiene and Tropical Medicine

(LSHTM), and the patient/relative/legal representative will retain the hard copy of the information sheet and consent form. As the consent form contains personal information, this will be stored encrypted and separate from the trial data and will not be used for any other purpose in the trial and will not be made available to anyone other than LSHTM Clinical Trials Unit (CTU) staff with responsibility for monitoring, the recruiting site investigators, regulatory agencies and Sponsor for inspection and audits.

2.4. Baseline data

The **entry form** (Appendix 2) will be completed on-line by the recruiting healthcare professional before randomisation to confirm eligibility and collect baseline data:

- Hospital details (name, country and admission date)
- Patient details (age, sex, contraindications, major comorbidities)
- Clinical signs/diagnosis (temperature, respiratory rate, heart rate, blood pressure, pneumonia, COVID-19 status)
- Randomisation details (name of person randomising, date of randomisation, randomisation number)

2.5. Randomisation and allocation concealment

Eligible patients will be randomised using an on-line randomisation service (which is accessed directly from the online trial database). Block randomisation will be used to ensure that each arm contains a similar number of participants. The REDCap randomisation module will be used to generate a randomisation scheme with the seed produced by a random number generator. Access to the randomisation system will be restricted to participating healthcare professionals. The randomisation number and treatment allocation will be provided on-screen via the on-line randomisation service and will also be emailed to the person randomising the patient. After recording the randomisation number in the medical record, the details of the allocated treatment will be provided. Clinicians are responsible for prescribing and administering the allocated treatment. Participants will receive the allocated treatment daily until the end of follow-up or if the responsible clinician decides to cease treatment.

2.6. Follow-up data

The **outcome form** (Appendix 3) will be used to collect outcome data at death, hospital discharge, or 28 days after randomisation, whichever occurs first. The data will be collected from the patient's medical records by clinical or research staff at the trial site. The primary outcome is in-hospital death (cause of death will be recorded). Secondary outcomes are myocardial infarction, cardiac failure, severe cardiac arrhythmia, myocarditis, respiratory failure including ARDS, viral pneumonitis, acute renal failure, sepsis, stroke,

gastrointestinal bleeding, receipt of non-invasive or mechanical ventilation requiring endotracheal intubation, ability to self-care at hospital discharge and time to hospital discharge. All patients randomised will be followed up irrespective of final COVID-19 diagnosis.

2.7. Withdrawal criteria

If a patient withdraws consent to participate they will be withdrawn from the trial. All pseudonymised data collected up to the point of withdrawal will be used in the analysis. If a patient wishes to discontinue the trial treatment but allows on-going data collection, the treatment will be discontinued and the trial data will be collected and used.

2.8. End of trial

Patients will be followed until death, discharge or 28 days after randomisation, whichever first. The trial ends 28 days after randomisation. An independent Data Monitoring Committee will advise the TSC about stopping the trial in line with their Charter but the TSC and Sponsor will make the final decision.

3. PHARMACOVIGILANCE

3.1. Adverse events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP).
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: <ul style="list-style-type: none"> • results in death; • is life-threatening; • requires inpatient hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability/incapacity • other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Investigator’s Brochure (IB).

Adverse events will be reported using an adverse event reporting form contained within the online trial database. As this trial is utilizing drugs with well known safety profiles and is being conducted in a pandemic situation, only those events which fulfill the ‘Serious Adverse Reaction’ criteria will be reported to LSHTM Clinical Trials Unit (CTU).

The LSHTM CTU will coordinate reporting of SARs/SUSARs to all relevant Regulatory Agencies, Ethics Committees and local investigators as per each participating country’s legal requirements.

3.2. Data Monitoring Committee

To protect the trial participants, an independent Data Monitoring Committee (DMC) has been appointed to oversee the trial. Membership includes expertise in medical care, clinical trials and statistics. The membership is listed in Appendix 5. An independent statistician will provide the analyses required by the DMC. If the DMC decides that any of the randomised comparisons provide evidence on mortality strong enough to affect national and international treatment strategies, it will inform the Trial Steering Committee

who will, as a matter of urgency, make the results available to the public and to the relevant authorities (e.g. WHO) and we will amend the remaining trial arms accordingly. The DMC Charter is in line with that proposed by the DAMOCLES Study Group (DAMOCLES Study Group 2005) and while the CRASH-19 trial is an open-label study, the research team and members of the TSC will only be permitted to conduct interim analyses without knowledge of the allocated trial treatment.

3.3. Trial Steering Committee

The TSC will include independent individuals and members from the Trial Management Group (TMG). The composition of the TSC is provided in the Appendix 5. The role of the TSC is to supervise the trial and to advise the Sponsor. In particular, the TSC will concentrate on the progress of the trial, adherence to the Protocol, participant safety, and consideration of new information. The TSC will agree the final Protocol and, throughout the trial, will take responsibility for:

- major decisions such as a need to change the protocol;
- monitoring and supervising the progress of the trial;
- reviewing relevant information from other sources;
- considering recommendations from the DMC;
- informing and advising the TMG on all aspects of the trial.

The TSC includes an experienced emergency medicine physician, clinical trialists, lead investigators, clinical representative from a low- and middle-income country (LMIC), and a lay representative. Face-to-face meetings or teleconferences will be held at regular intervals determined by need, but no less than once a year. A TSC Charter, which will detail how it will conduct its business, will be agreed at the first meeting.

4. DATA ANALYSIS AND MANAGEMENT

4.1. Sample size

Because of the scale of the COVID-19 pandemic, there is no shortage of potentially eligible patients. Two main factors determine the number of patients needed in a trial: (1) the event rate and (2) the treatment effect. Data from the UK show that about 12% of patients hospitalized with COVID-19 infection die from the disease. Because the risk of death increases with age and we are limiting recruitment to patients aged ≥ 40 years the risk of death is likely to be higher. We also expect the risk of death to be higher in low- and middle-income settings where the provision of intensive care facilities is limited. Taken together, we expect a case fatality of about 15%. Because even a 3% survival advantage for interventions as simple and widely practicable as those being evaluated in this trial would represent a worthwhile benefit, the CRASH-19 trial has been planned to be able to detect a benefit of this size. If the real mortality difference is 15% vs 12% then

a trial with about 10,000 patients will have over 90% power to detect a difference of this magnitude at the 0.01 level of significance. Because this is a newly emerging disease, assumptions about the event rate are based on limited data and so we will allow for the sample size to be increased or decreased if the event rate observed in the trial differs substantially from the anticipated event rate.

4.2. Statistics and Data analysis

All statistical analyses will be conducted by LSHTM CTU using STATA (version 16). A detailed Statistical Analysis Plan setting out full details of the proposed analyses will be published separately. The primary analysis will be a factorial analysis comparing each active treatment arm to the control arm on an intention to treat basis, irrespective of whether patients received any other active treatment. We will assess whether there is an interaction between the active treatment effects on the primary outcome, presenting the size of the interaction term with a measure of precision. Results will be presented as effect estimates (relative risks and absolute risks) with a measure of precision (95% confidence intervals). A survival analysis will be conducted using time-to-event data. We will present hazard ratios, log-rank tests and Kaplan-Meier plots. If sufficient patients are recruited, subgroup analyses will be conducted stratifying patients on key prognostic factors including age, sex and comorbidities. Stratum-specific effect estimates, 95% confidence intervals and heterogeneity p-values will be presented.

4.3. Data management

Data will be collected at each site by local investigators and sent to the LSHTM CTU. Only data outlined on the entry, outcome and adverse event forms will be collected in this trial. To allow for variation in available technology for data transfer and to minimise cross infection, a variety of data collection methods will be used. Data will be collected by the investigator on paper or electronic case report forms (CRFs) and transmitted to the LSHTM CTU either by email or by entering the data directly into the trial database. Original paper CRFs where used, will remain at each trial site. The data will be used in accordance with local regulations and ethics approval. Investigators/institutions are required to provide access to source data for trial-related monitoring, audits, ethics committee review and inspection. All trial related and source documents must be kept for at least five years after the end of the trial.

5. ETHICAL, REGULATORY AND OPERATIONAL CONSIDERATIONS

5.1. Research Ethics Committee review

Fast-track review will be sought from national and local research ethics committees.

5.2. Monitoring, audit and inspection

In accordance with the principles of Good Clinical Practice and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of hospitalised patients with suspected or confirmed COVID-19 infection who are included in this trial and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- to minimise the burden on busy healthcare professionals working in an overstretched hospital during this major pandemic
- to ensure that suitable patients have access to the trial treatment without impacting or delaying other aspects of their emergency care
- to provide information on the trial to patients and healthcare professionals in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care
- to allow individual clinicians to use their judgement about whether any of the treatment arms are not suitable for the patient
- to collect comprehensive information on the mortality and disease status

In assessing any risks to patient safety and wellbeing, a key principle is that of proportionality. Risks associated with participation in the trial are considered in the context of usual care. At present, there are no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

The trial will be conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP), current approved protocol, and relevant regulations. Serious breaches of GCP will be managed in accordance with each country's regulatory requirements. In the context of this pandemic, visits to trial sites is generally not appropriate as they could increase the risks of spreading infection, and in the context of this trial they generally would not influence the reliability of the trial results or the well-being of the participants. All coordinating centres and site trial teams will be trained in the trial procedures. Central monitoring methods will be used by the CTU. Data management and statistical checks of data (central statistical monitoring) will be done to ensure trial participants meet the inclusion criteria and trial treatment is administered in line with the protocol. Event rates for primary and secondary outcomes will be monitored. Sites with higher or lower than expected event rates will be selected for further monitoring. Quantitative variables (systolic blood pressure, heart rate, respiratory rate, and temperature) will be

monitored to check the accuracy of the data. For example, the coefficient of variation for the data at each site will be examined and those where there is any reason for concern will be selected for further monitoring. Additional central monitoring will be carried out at sites flagged as high risk on central statistical monitoring and onsite monitoring done where it is safe to do so. Source data verification will be done on about 10% of the primary outcome data. Site self-monitoring will be carried out where indicated by central monitoring. This will involve the PI/delegate at site monitoring themselves against a standardised checklist. A full monitoring plan will be developed.

Source documents for the study constitute the records held in the study main database and the patient clinical records. These will be retained for at least 10 years from the completion of the study. 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 epidemic).

LSHTM CTU will require investigators and their institutions to provide access to source data and all trial related documents for monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents including medical records, original consent forms and original CRFs must be kept safely. Investigators must plan in advance of the trial start where the trial-related documents will be stored and how they will be accessed.

5.3. Trial sponsor and coordination

The London School of Hygiene and Tropical Medicine (LSHTM) is the trial sponsor. The trial will be coordinated from the LSHTM CTU. Coordination of the trial within each country will be supported by a National Coordinating Investigator.

5.4. Indemnity

LSHTM accepts responsibility attached to its sponsorship of the trial and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of the trial procedures.

5.5. Supply of trial treatments

The trial treatments will be supplied by the hospital pharmacy at each trial site from routine clinical supplies. The interventions will be sourced within each participating country and costs of the trial treatments will be covered by LSHTM where patients are responsible for the cost of treatments. The original drug label will not be changed. All aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medicines. Treatment administered to randomised participants will be by prescription.

5.6. Funding

This trial is supported by a grant from LSHTM. The LSHTM CTU is supported by NIHR Clinical Trials Unit Support Funding.

5.7. Dissemination

All trial data will be shared in line with the Joint statement on sharing research data and findings relevant to the novel coronavirus outbreak. Specifically, we will ensure that:

- all peer-reviewed research publications relevant to the outbreak are made immediately open access, or freely available at least for the duration of the outbreak
- research results relevant to the outbreak are shared immediately with the WHO upon journal submission, by the journal with author knowledge or by us
- research findings are made available via preprint servers before journal publication, or via platforms that make papers openly accessible before peer review, with clear statements regarding the availability of underlying data
- we will share interim and final research data relating to the outbreak, together with protocols and standards used to collect the data, as rapidly and widely as possible - including with public health and research communities and the WHO
- authors are clear that data or preprints shared ahead of submission will not pre-empt its publication in these journals

We will try to publish the trial protocol, statistical analysis plan and the CRASH-19 trial results in fast track peer-reviewed journals. All publications will follow relevant external guidance such as the *'Uniform Requirements for Submission of Manuscripts to Biomedical Journals'* issued by the International Committee of Medical Journal Editors (ICMJE) (2008 update) and the CONSORT statement (Moher 2001). Links to the publication will be provided in all applicable trial registers. Dissemination of results to patients and the public will take place via the media and relevant public health organisations. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients. The success of the trial will be dependent entirely upon the collaboration of the nurses, doctors and other health professionals in the participating hospitals and those who hold key responsibility for the trial. Hence, the credit for the study will be assigned to the key collaborator(s) from each participating site, as it is crucial that those who carry out the work are given credit for it. The results of the trial will be disseminated rapidly. As many sites will contribute to this trial, individual sites cannot restrict the publication of the manuscript relating to the outcomes of this trial. All anonymised data from this trial will be made freely available on our data sharing site: <http://freebird.lshtm.ac.uk>.

6. REFERENCES

- 1 Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System A Review. *JAMA Cardiol* 2020. DOI:10.1001/jamacardio.2020.1286.
- 2 Shi S, Qin M, Shen B, *et al.* Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; published online March 25. DOI:10.1001/jamacardio.2020.0950.
- 3 Guo T, Fan Y, Chen M, *et al.* Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; published online March 27. DOI:10.1001/jamacardio.2020.1017.
- 4 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **0**. DOI:10.1016/S0140-6736(20)30628-0.
- 5 Wu C, Chen X, Cai Y, *et al.* Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; published online March 13. DOI:10.1001/jamainternmed.2020.0994.
- 6 Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; : 1–3.
- 7 Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020; published online March. DOI:10.1016/j.pcad.2020.03.001.
- 8 Inciardi RM, Lupi L, Zaccone G, *et al.* Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; published online March 27. DOI:10.1001/jamacardio.2020.1096.
- 9 Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. *N Engl J Med* 2004; **351**: 2611–8.
- 10 Warren-Gash C, Hayward AC, Hemingway H, *et al.* Influenza infection and risk of acute myocardial infarction in england and wales: A CALIBER self-controlled case series study. *J Infect Dis* 2012. DOI:10.1093/infdis/jis597.
- 11 Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect. Dis.* 2009; **9**: 601–10.
- 12 Hingorani AD, Cross J, Kharbanda RK, *et al.* Acute systemic inflammation impairs endothelium-dependent dilatation in humans. *Circulation* 2000; **102**: 994–9.
- 13 Haidari M, Wyde PR, Litovsky S, *et al.* Influenza virus directly infects, inflames, and resides in the arteries of atherosclerotic and normal mice. *Atherosclerosis* 2010; **208**: 90–6.
- 14 Madjid M, Vela D, Khalili-Tabrizi H, Casscells SW, Litovsky S. Systemic infections cause exaggerated local inflammation in atherosclerotic coronary arteries: Clues to the triggering effect of acute infections on acute coronary syndromes. *Texas Hear Inst J* 2007; **34**: 11–8.
- 15 Matthay MA, Zemans RL, Zimmerman GA, *et al.* Acute respiratory distress syndrome. *Nat Rev Dis Prim* 2018; **5**: 18.
- 16 Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* 2020; : 1–2.
- 17 Kuba K, Imai Y, Rao S, *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; **11**: 875–9.
- 18 Kuster G, Pfister O, Bukard T, *et al.* SARS-CoV2: Should Inhibitors of the Renin-Angiotensin System Be Withdrawn in Patients With COVID-19? - PubMed. *Eur Hear J* 2020. <https://pubmed.ncbi.nlm.nih.gov/32196087/> (accessed March 23, 2020).
- 19 Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* 2020; : NEJMSr2005760.
- 20 Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020; : ddr.21656.

- 21 Jacobson JR, Barnard JW, Grigoryev DN, Ma SF, Tudor RM, Garcia JGN. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. *Am J Physiol - Lung Cell Mol Physiol* 2005; **288**. DOI:10.1152/ajplung.00354.2004.
- 22 Shyamsundar M, McKeown STW, O’Kane CM, *et al*. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med* 2009; **179**: 1107–14.
- 23 Janda S, Young A, FitzGerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: A systematic review and meta-analysis. *J Crit Care* 2010; **25**: 656.e7-656.e22.
- 24 McAuley DF, Laffey JG, O’Kane CM, *et al*. Simvastatin in the Acute Respiratory Distress Syndrome. *N Engl J Med* 2014; **371**: 1695–703.
- 25 Calfee CS, Delucchi KL, Sinha P, *et al*. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018; **6**: 691–8.
- 26 CRASH-2 trial collaborators, Shakur H, Roberts I, *et al*. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet (London, England)* 2010; **376**: 23–32.
- 27 CRASH-3 Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet* 2019; **394**: 1713–23.

7. APPENDICES

Appendix 1: Contraindications to trial treatments

Please refer to the full data sheet/Summary of Product Characteristics (SmPc). Below is a summary of key contraindications.

Aspirin

Previous anaphylactic reaction with aspirin or NSAID; previous urticaria with aspirin or NSAIDs; previous bronchospasm with aspirin or NSAID; children under 16 years (risk of Reye's syndrome); active peptic ulceration; bleeding disorders; haemophilia; previous peptic ulceration (analgesic dose); severe cardiac failure (analgesic dose).

Losartan

Combination therapy with angiotensin-II receptor antagonist and aliskiren in patients with an eGFR less than 60 mL/minute/1.73 m² or diabetes mellitus; severe hepatic impairment; 2nd and 3rd trimester of pregnancy; hypersensitivity to the active substance or to any of the excipients (see SmPC).

Simvastatin

Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) level > 100iu/L; unexplained persistent isolated elevations of serum transaminases; pregnancy and lactation; In patients with severe renal impairment (Creatinine Clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered; history of rhabdomyolysis associated with statin use, concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat); Concomitant administration of gemfibrozil, ciclosporin or danazol; In patients with Homozygous Familial Hypercholesterolemia, concomitant administration of lomitapide with doses > 40 mg simvastatin; Hypersensitivity to the active substance or to any of the excipients (see SmPC).

Appendix 2: Entry form

ENTRY FORM



PLEASE COMPLETE 1-30 BEFORE RANDOMISING THE PATIENT

ABOUT YOUR HOSPITAL (please ensure all information below is contained in the medical records)

1. Country		2. Hospital name, ID	
------------	--	----------------------	--

ABOUT THE PATIENT (circle one answer where options are given)

3. Date of admission to hospital	day	month	year	4. Sex	MALE	FEMALE
5. Age (approximate if unknown)	years			6. Current smoker?	YES	NO

7. COVID-19 status	SUSPECTED		CONFIRMED	NOT SUSPECTED (do not randomise)		
8. Difficulty breathing	YES	NO	9. Signs of hypoxia?		YES	NO
10. Breathing assisted by	NONE	OXYGEN ONLY	CPAP	BIPAP	MECHANICAL VENTILATION (do not randomise)	
11. Chronic respiratory disease	YES	NO	17. Liver disease		YES	NO
12. Cardiovascular disease	YES	NO	18. Cancer		YES	NO
13. Immunocompromised	YES	NO	19. Neurological disease		YES	NO
14. Body mass index >40 (estimated)	YES	NO	20. Current active infection		YES	NO
15. Diabetes mellitus	YES	NO	21. Other major disease		YES	NO
16. Renal failure	YES	NO	a. If Yes, describe			
22. Terminally ill / approaching end of life	YES	NO	If YES, do not randomise			
23. Any clinical indication for or contraindication to aspirin, losartan or statins			YES	NO	If YES, do not randomise	
24. Consent type	PATIENT	PERSONAL REPRESENTATIVE		PROFESSIONAL REPRESENTATIVE		
25. Blood Pressure (mmHg)	a. Systolic	b. Diastolic		26. Temperature (°C)		
27. Heart Rate (beats per minute)	28. Respiratory Rate (breaths per minute)					
29. Chest X ray / Chest CT results	NOT AVAILABLE	NORMAL	PNEUMONIA	OTHER		

30. Eligible? (age ≥ 40, confirmed/suspected acute COVID-19, not pregnant, no contraindication to trial drugs, not on mechanical ventilation and not terminally ill / approaching end of life)				YES	NO	If YES, go online and upload baseline data to randomise		
31. Insert RANDOMISATION number						Record from randomisation screen. Write number in medical records. Prescribe and give intervention(s) immediately after randomisation.		
32. Intervention(s) to be given (for site use only)	ASPIRIN	LOSARTAN	SIMVASTATIN	ASPIRIN + LOSARTAN	ASPIRIN + SIMVASTATIN	LOSARTAN + SIMVASTATIN	ASPIRIN + LOSARTAN + SIMVASTATIN	STANDARD CARE ONLY
33. Date of randomisation	day	month	year	34. Time of randomisation (24-hour clock)		hours	minutes	
35. Name of person randomising	first/last name			36. Signature				
SITE ADMIN - NON TRIAL DATA - USED ONLY FOR IDENTIFYING PATIENT FOR HOSPITAL FOLLOW UP ONLY								
37. PATIENT DETAILS	a) Patient name	first/last name			c) Hospital ID number			
	b) Date of birth	day	month	year	d) Ward admitted to			

CRASH-19 – Entry form Version 1.0 [15 April 2020]

Appendix 3: Outcome form

OUTCOME FORM



PLEASE COMPLETE AT DEATH, DISCHARGE OR DAY 28 WHICHEVER COMES FIRST

1. HOSPITAL NAME, ID																																																													
2. PATIENT RANDOMISATION NUMBER																																																													
3. OUTCOME																																																													
3.1 DEATH IN HOSPITAL				3.2 PATIENT ALIVE <i>(Select one and provide date)</i>																																																									
a) Date of death				a) Still in this hospital now <i>(28 days after randomisation) – Date</i>																																																									
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; text-align: center;">DAY (DD)</td> <td style="width: 25%; text-align: center;">MONTH (MM)</td> <td style="width: 25%; text-align: center;">YEAR (YYYY)</td> <td style="width: 25%;"></td> </tr> </table>				DAY (DD)	MONTH (MM)	YEAR (YYYY)		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%; text-align: center;">DAY (DD)</td> <td style="width: 33%; text-align: center;">MONTH (MM)</td> <td style="width: 33%; text-align: center;">YEAR (YYYY)</td> </tr> </table>				DAY (DD)	MONTH (MM)	YEAR (YYYY)																																															
DAY (DD)	MONTH (MM)	YEAR (YYYY)																																																											
DAY (DD)	MONTH (MM)	YEAR (YYYY)																																																											
b) Time of death (24hr)				b) Transferred to another hospital – Date of discharge																																																									
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; text-align: center;">HOUR (HH)</td> <td style="width: 25%; text-align: center;">MIN (MM)</td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				HOUR (HH)	MIN (MM)			<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%; text-align: center;">DAY (DD)</td> <td style="width: 33%; text-align: center;">MONTH (MM)</td> <td style="width: 33%; text-align: center;">YEAR (YYYY)</td> </tr> </table>				DAY (DD)	MONTH (MM)	YEAR (YYYY)																																															
HOUR (HH)	MIN (MM)																																																												
DAY (DD)	MONTH (MM)	YEAR (YYYY)																																																											
c) Primary Cause of death <i>(tick one option)</i>				c) Discharged home – Date of discharge																																																									
<input type="checkbox"/> Respiratory failure incl. ARDS <input type="checkbox"/> Congestive cardiac failure <input type="checkbox"/> Myocardial Infarction <input type="checkbox"/> Sepsis <input type="checkbox"/> Multi organ failure <input type="checkbox"/> Other, describe here (only one) _____				<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%; text-align: center;">DAY (DD)</td> <td style="width: 33%; text-align: center;">MONTH (MM)</td> <td style="width: 33%; text-align: center;">YEAR (YYYY)</td> </tr> </table>				DAY (DD)	MONTH (MM)	YEAR (YYYY)																																																			
DAY (DD)	MONTH (MM)	YEAR (YYYY)																																																											
4. MANAGEMENT				3.3 Ability to self-care at discharge versus before illness <i>(circle one):</i>																																																									
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%;">a) Admitted to ICU</td> <td style="width: 10%; text-align: center;">YES</td> <td style="width: 10%; text-align: center;">NO</td> <td style="width: 55%;">Needed, not available</td> </tr> <tr> <td colspan="4"><i>i) if yes, days in ICU (if none, write '0')</i></td> </tr> <tr> <td>b) Ventilatory support</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td>Needed, not available</td> </tr> <tr> <td colspan="4"><i>i) Mechanical ventilation</i></td> </tr> <tr> <td></td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td>Needed, not available</td> </tr> <tr> <td colspan="4"><i>ii) CPAP/BIPAP</i></td> </tr> <tr> <td></td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td>Needed, not available</td> </tr> <tr> <td>c) Corticosteroids</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td rowspan="7"></td> </tr> <tr> <td>d) Antimalarial</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>e) Antiviral</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>f) Antibiotics</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>g) Vasopressor/inotrope</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> </table>				a) Admitted to ICU	YES	NO	Needed, not available	<i>i) if yes, days in ICU (if none, write '0')</i>				b) Ventilatory support	YES	NO	Needed, not available	<i>i) Mechanical ventilation</i>					YES	NO	Needed, not available	<i>ii) CPAP/BIPAP</i>					YES	NO	Needed, not available	c) Corticosteroids	YES	NO		d) Antimalarial	YES	NO	e) Antiviral	YES	NO	f) Antibiotics	YES	NO	g) Vasopressor/inotrope	YES	NO	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; text-align: center;">SAME AS BEFORE ILLNESS</td> <td style="width: 20%; text-align: center;">WORSE</td> <td style="width: 20%; text-align: center;">BETTER</td> </tr> </table>				SAME AS BEFORE ILLNESS	WORSE	BETTER							
a) Admitted to ICU	YES	NO	Needed, not available																																																										
<i>i) if yes, days in ICU (if none, write '0')</i>																																																													
b) Ventilatory support	YES	NO	Needed, not available																																																										
<i>i) Mechanical ventilation</i>																																																													
	YES	NO	Needed, not available																																																										
<i>ii) CPAP/BIPAP</i>																																																													
	YES	NO	Needed, not available																																																										
c) Corticosteroids	YES	NO																																																											
d) Antimalarial	YES	NO																																																											
e) Antiviral	YES	NO																																																											
f) Antibiotics	YES	NO																																																											
g) Vasopressor/inotrope	YES	NO																																																											
SAME AS BEFORE ILLNESS	WORSE	BETTER																																																											
6. COMPLICATIONS				5. TRIAL TREATMENT GIVEN																																																									
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;">a) Myocardial infarction</td> <td style="width: 15%; text-align: center;">YES</td> <td style="width: 15%; text-align: center;">NO</td> </tr> <tr> <td>b) Congestive cardiac failure</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>c) Severe cardiac arrhythmia</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>d) Myocarditis</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>e) Respiratory failure including ARDS</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>f) Viral pneumonitis</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>g) Acute renal failure</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>h) Sepsis</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>i) Stroke</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>j) Gastrointestinal bleeding</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> </tr> </table>				a) Myocardial infarction	YES	NO	b) Congestive cardiac failure	YES	NO	c) Severe cardiac arrhythmia	YES	NO	d) Myocarditis	YES	NO	e) Respiratory failure including ARDS	YES	NO	f) Viral pneumonitis	YES	NO	g) Acute renal failure	YES	NO	h) Sepsis	YES	NO	i) Stroke	YES	NO	j) Gastrointestinal bleeding	YES	NO	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="4" style="padding: 5px;"><i>if standard care only, skip to Q6</i></td> </tr> <tr> <td colspan="3"></td> <td style="text-align: center;">Total number of days</td> </tr> <tr> <td style="width: 25%;">a) Aspirin 150 mg</td> <td style="width: 10%; text-align: center;">YES</td> <td style="width: 10%; text-align: center;">NO</td> <td style="width: 55%;"></td> </tr> <tr> <td>b) Losartan 100 mg</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td></td> </tr> <tr> <td>c) Losartan <100 mg</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td></td> </tr> <tr> <td>d) Simvastatin 80 mg</td> <td style="text-align: center;">YES</td> <td style="text-align: center;">NO</td> <td></td> </tr> </table>				<i>if standard care only, skip to Q6</i>							Total number of days	a) Aspirin 150 mg	YES	NO		b) Losartan 100 mg	YES	NO		c) Losartan <100 mg	YES	NO		d) Simvastatin 80 mg	YES	NO	
a) Myocardial infarction	YES	NO																																																											
b) Congestive cardiac failure	YES	NO																																																											
c) Severe cardiac arrhythmia	YES	NO																																																											
d) Myocarditis	YES	NO																																																											
e) Respiratory failure including ARDS	YES	NO																																																											
f) Viral pneumonitis	YES	NO																																																											
g) Acute renal failure	YES	NO																																																											
h) Sepsis	YES	NO																																																											
i) Stroke	YES	NO																																																											
j) Gastrointestinal bleeding	YES	NO																																																											
<i>if standard care only, skip to Q6</i>																																																													
			Total number of days																																																										
a) Aspirin 150 mg	YES	NO																																																											
b) Losartan 100 mg	YES	NO																																																											
c) Losartan <100 mg	YES	NO																																																											
d) Simvastatin 80 mg	YES	NO																																																											
7. PERSON COMPLETING FORM				6. COMPLICATIONS																																																									
a) Name				a) Myocardial infarction																																																									
				<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;"></td> <td style="width: 15%; text-align: center;">YES</td> <td style="width: 15%; text-align: center;">NO</td> </tr> </table>					YES	NO																																																			
	YES	NO																																																											
b) Job title				b) Congestive cardiac failure																																																									
				<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;"></td> <td style="width: 15%; text-align: center;">YES</td> <td style="width: 15%; text-align: center;">NO</td> </tr> </table>					YES	NO																																																			
	YES	NO																																																											
c) Signature				c) Severe cardiac arrhythmia																																																									
				<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;"></td> <td style="width: 15%; text-align: center;">YES</td> <td style="width: 15%; text-align: center;">NO</td> </tr> </table>					YES	NO																																																			
	YES	NO																																																											
d) Date				d) Myocarditis																																																									
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%; text-align: center;">DAY (DD)</td> <td style="width: 33%; text-align: center;">MONTH (MM)</td> <td style="width: 33%; text-align: center;">YEAR (YYYY)</td> </tr> </table>				DAY (DD)	MONTH (MM)	YEAR (YYYY)	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;"></td> <td style="width: 15%; text-align: center;">YES</td> <td style="width: 15%; text-align: center;">NO</td> </tr> </table>					YES	NO																																																
DAY (DD)	MONTH (MM)	YEAR (YYYY)																																																											
	YES	NO																																																											

Appendix 4: Information sheet and consent form

STUDY INFORMATION FOR PARTICIPANTS AND THEIR REPRESENTATIVES

Study Title	Aspirin, losartan and simvastatin in hospitalised COVID-19 patients: a multinational randomised open-label factorial trial (CRASH-19)
Leaflet Version Number / Date	

Invitation to take part:

This hospital is taking part in an international study to find treatments for COVID-19 infection. We are inviting adults aged 40 years and older who have been admitted to hospital with suspected or confirmed COVID-19 infection to join this research study. This form gives information about the study including the aims, risks and benefits of taking part. If you agree to take part, we will ask you to sign a consent form.

WHAT YOU SHOULD KNOW ABOUT THIS RESEARCH STUDY:

1) Why is this research being done?

Your doctors suspect, or have confirmed, that you have an infection called COVID-19. This is caused by a type of virus called SARS-CoV-2, or coronavirus for short. About 8 out of 10 patients who get coronavirus get better without coming to hospital. Of those who are admitted to hospital, most also get better, but some may need more intensive medical care including oxygen or ventilation before they do so. However, a few percent do not get better.

There are currently no drugs to treat COVID-19 although there are several being developed. This study is being done to find out if by giving additional treatments to support the heart and lungs while patients are ill, we can improve how well they do.

2) What is the purpose of this study?

This study aims to compare three different treatments that are known to help people with heart and breathing problems and which may be useful for patients with COVID-19. Although these treatments are promising, nobody knows if either will be more effective in helping patients recover than the usual standard of care at your hospital (which everyone will receive).

The treatments which may be given to you, in addition to the usual standard of care at your hospital, are:

- Aspirin (commonly used to prevent heart attacks and strokes)
- Losartan (commonly used to treat high blood pressure, protect the kidneys and reduce strain on the heart)
- Simvastatin (commonly used to lower cholesterol)
- Combination of aspirin and/or losartan and/or simvastatin

- Standard care with no additional treatment

3) Who is doing the study?

The study is run by a team of researchers at the London School of Hygiene and Tropical Medicine (University of London) in the United Kingdom. Doctors and nurses in hospitals around the world are also taking part.

4) Who is being included in the study?

Patients may be included in this study if they are at least 40 years of age and the doctor suspects or has confirmed COVID-19 infection. Patients will not be included if the doctor thinks there is a particular reason why the study treatments are not suitable, for example you are known to have an allergy to one of them. Patients already on a mechanical breathing machine cannot take part either. About 10,000 patients worldwide will be taking part in this study. It is up to you to decide if you wish to take part or not.

5) What happens next if I agree to be included in this study?

If you decide to join, you will be asked to sign the consent form. Brief details about your health and medical conditions will then be entered into a computer. The computer will then randomly decide which of the treatment groups to put you into. In all cases this will include the usual standard of care for your hospital. It may also include an additional treatment, which will be given by mouth or if you are too unwell, by a tube in your gut which is feeding you. Neither you nor your doctors can choose which of the treatments you will be given. If you have been allocated one, two or three of the treatments, you will receive them once per day for a maximum of 28 days or until you are discharged from hospital whichever is sooner. Additional information about your health will be recorded and entered into a computer but no additional visits will be required after you leave the hospital.

6) What are the possible benefits of being in the study?

We do not know if any of the treatments being tested will have additional benefits. Your study treatment may or may not help you personally, but this study should help future patients.

7) What are the possible risks of being in the study?

Apart from the known side effects of these treatments (which may include indigestion, unusual bleeding and dizziness), there is the unlikely possibility of a severe reaction to a study drug. Please ask your hospital doctor if you would like more information. Once you have been included in the study, you and your doctors will know which treatment the computer has allocated for you. Your doctors are familiar with the use of the study drugs and will be aware of whether there are any particular side effects that they should look out for.

8) Can I stop the study treatment or my participation early?

Yes. If you or your doctor want to stop the study treatment at any time, then you are free to do so. If you decide that you do not wish any more information to be collected about you, you are free to say so (although information that has been collected up to that point will continue to be analysed by the research team).

9) If I have any questions or problems, who can I contact?

If you have any questions or problems please speak to your hospital medical team. Further information about the study is also available on the study website (<http://crash19.lshtm.ac.uk/>).

10) What information do you keep private?

All information about you and your health will be kept private. The only people allowed to look at the information will be the doctors who are running the study, the staff at the study coordinating centre from the London School of Hygiene and Tropical Medicine (University of London), and the regulatory authorities who check that the study is being carried out correctly. Some hospitals may not be able to store a copy of the paper consent form due the risk of spreading coronavirus. In this case a copy of the consent form which will have your name and signature on it will be stored electronically at the the study coordinating centre in London. This information will be handled confidentially and will not be passed on to anyone else.. Your name will not be used when the results are published. A privacy notice is on the study website.

11) Do I have to take part?

It is up to you to decide to join the study, joining is voluntary. Your decision whether to take part will not affect the care you receive at this hospital.

12) Are there any financial costs or payments?

The study treatment is free. Neither you nor your medical staff will be paid for your participation in this study.

13) What else can you tell me?

The study is funded by the London School of Hygiene and Tropical Medicine, not the makers of any of the study drugs. If we find out any new information that might affect your decision to stay in the study, we will give it to you. If something goes wrong and you are harmed during the study, the London School of Hygiene & Tropical Medicine would be responsible for claims for any non-negligent harm. To look after your interests, this study has been carefully checked by an independent group of people called a Research Ethics Committee [Insert Name]. They agreed that it is okay [for us to do this study]. The final results of the study will be available on the study website once published.

PARTICIPANT CONSENT FORM

Study Title: Aspirin, losartan and simvastatin in hospitalised COVID-19 patients: a multinational randomised open-label factorial trial (CRASH-19)

Hospital Name: (use CAPITALS)	
Participant Name: (use CAPITALS)	
Randomisation Number: (enter after randomisation)	

1. Information about the study has been provided to me: I confirm that I have read (or had read to me) and understood the Participant Information Leaflet (**VERSION NO. & DATE**) and I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. Voluntary participation: I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. Access to study data about me: I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorised individuals from this hospital, the London School of Hygiene and Tropical Medicine, and regulatory authorities to check that the study is being carried out correctly.

4. Access to my medical information: I agree that medical information (without my personal information) collected by the doctors and nurses at hospitals which provide me with care can be sent to the London School of Hygiene & Tropical Medicine. I also agree that this information which cannot identify me in anyway can also be shared with other researchers on a public database.

5. Data stored on computer: I understand that information about my progress in the study will be recorded on a database, and that this data will be stored on computers supervised by the London School of Hygiene and Tropical Medicine. I understand that this information will be kept securely and confidentially.

6. Access to this consent form: I give permission for a digital copy of this consent form, which contains my name, to be made available to the London School of Hygiene & Tropical Medicine if necessary.

7. Agreement to take part: I agree to take part in the above study.

..... Name of participant (Use CAPITALS) Signature/ Thumbprint or other mark (if unable to sign)/...../..... Today's date
---	---	-----------------------------------

..... Name of consent taker (Use CAPITALS) Signature/...../..... Today's date
---	--------------------	-----------------------------------

If participant is not able to read the text and/or sign for themselves but has capacity to give consent:

I witnessed accurate reading of the consent form to the potential participant, who could ask any questions and got satisfactory replies. I confirm that they gave their consent freely.

..... Name of Witness (Use CAPITALS) Signature/...../..... Today's date
---	--------------------	-----------------------------------

**1 copy for participant; 1 copy to be kept in medical notes; Original for Investigator's site file. If high risk of cross-infection from storage of consent form, electronic copy to be sent to LSHTM; copy for participant*

REPRESENTATIVE CONSENT FORM

Study Title: Aspirin, losartan and simvastatin in hospitalised COVID-19 patients: a multinational randomised open-label factorial trial (CRASH-19)

Hospital Name: (use CAPITALS)	
Participant Name: (use CAPITALS)	
Randomisation Number: (enter after randomisation)	

If participant temporarily lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure, confusion or need for immediate ventilation):

- I have read the information (or had it read to me) and had an opportunity to ask questions.
- I understand that the participant will be asked to confirm their consent as soon as they have the capacity to do so and that if they wish, they will be able to withdraw from the study without it affecting their medical care.
- I believe that if they were able to, the participant would consent to take part in this study.

..... Name of Representative (Use CAPITALS) Signature / Thumbprint or other mark (if unable to sign)/...../..... Today's date
--	--	-----------------------------------

.....
 Relationship to participant

..... Name of consent taker (Use CAPITALS) Signature/...../..... Today's date
---	--------------------	-----------------------------------

**1 copy for Representative; 1 copy to be kept in medical notes; Original for Investigator's site file. If high risk of cross-infection from storage of consent form, electronic copy to be sent to LSHTM; 1 copy for representative*

Appendix 5: Trial organisation and responsibilities

<p>Data Monitoring Committee</p>	<p>Professor Anthony Rodgers (Chair) Head, Cardiovascular Program and Professor of Global Health, The George Institute for Global Health Head Office: Level 5, 1 King St Newtown NSW 2042 Australia Postal Address: PO Box M201 Missenden Rd NSW 2050 Australia T +61 2 8052 4375 Email: arodgers@georgeinstitute.org</p> <p>Professor Akin Osibogun, Public Health Physician, Lagos University Teaching Hospital, Ishaga Road, Idi-Araba, Lagos, Nigeria. Email: akinosibogun@yahoo.co.uk</p> <p>Professor Gavin Perkins Director, Warwick Clinical Trials Unit Warwick Medical School, University of Warwick Coventry CV4 7AL Email: G.D.Perkins@warwick.ac.uk</p> <p>Professor Deborah J. Cook Department of Medicine and Clinical Epidemiology & Biostatistics McMaster University, McMaster University Medical Centre 1200 Main Street West, Hamilton, ON L8N 3Z5 Email: debcook@mcmaster.ca</p>
<p>Trial Steering Committee</p>	<p>Professor John Cleland (Chair), Director of the Robertson Centre for Biostatistics and Clinical Trials University of Glasgow, UK Email: John.Cleland@glasgow.ac.uk</p> <p>Professor Oyewale Tomori, Virologist and Immediate Past President, Nigerian Academy of Science. Redeemers University, Ede, Nigeria, Email: oyewaletomori@gmail.com</p> <p>Dr Angèle Gayet-Ageron, University Hospital of Geneva, Rue Gabrielle Perret-Gentil 4, (ex - 24 rue Micheli-du-Crest), 1211 Geneva 14, Switzerland Email: Angele.Gayet-Ageron@hcuge.ch T. +41 22 372 90 27 M. +41 79 553 46 50</p> <p>Professor Muhammad Shoaib Shafi Senior Vice President, The College of Physicians and Surgeons Pakistan (CPSP) Head of Medical Unit-II</p>

	<p>Benazir Bhutto Hospital, Rawalpindi, Pakistan Phone: 92-0300-5005478 E-mail: shaficlinic@yahoo.com</p>
Protocol Development Committee	<p>Professor Rizwana Chaudhri, Principal Scientist, Global Institute of Human Development, Shifa Tameer-e-Millat University, Rawalpindi, Pakistan</p> <p>Professor Temitayo Shokunbi, Professor of Anatomy, College of Medicine, University of Ibadan, Nigeria</p> <p>Professor Danny McAuley, Professor of Intensive Care Medicine at the Wellcome-Wolfson Institute for Experimental Medicine, Queen's University of Belfast, and Consultant in Intensive Care Medicine at the Royal Victoria Hospital, Belfast.UK</p> <p>Dr Charlotte Warren-Gash, Associate Professor of Epidemiology and an Honorary Consultant in Public Health, LSHTM. UK</p> <p>Dr Aasia Kiyani, Trial Coordinator, Global Institute of Human Development, Shifa Tameer-e-Millat University, Rawalpindi, Pakistan</p> <p>Dr Kiran Javaid, Assistant Trial Coordinator, Global Institute of Human Development, Shifa Tameer-e-Millat University, Rawalpindi, Pakistan</p> <p>Dr Folasade Adenike Bello, Co-Director, LSHTM- College of Medicine, University of Ibadan Collaboration, Nigeria</p> <p>Professor Oladapo Oalyemi, Co-Director, LSHTM- College of Medicine, University of Ibadan Collaboration, Nigeria</p> <p>Ms. Amy Brenner, Research Fellow and Epidemiologist, LSHTM, UK</p> <p>Professor Ian Roberts, Co-Director, Clinical Trials Unit, LSHTM, UK</p> <p>Professor Haleema Shakur-Still, Co-Director, Clinical Trials Unit, LSHTM, UK</p>
Co-Chief Investigator	<p>Ian Roberts Professor of Epidemiology and Public Health Email: ian.roberts@Lshtm.ac.uk Phone: 020 7958 8128 Fax: 020 7299 4663</p>
Co-Chief Investigator	<p>Haleema Shakur-Still Professor of Global Health Clinical Trials Email: haleema.shakur@Lshtm.ac.uk Phone: 020 7958 8113 Fax: 020 7299 4663</p>

Sponsor's Legal Representative	<p>Patricia Henley Head of Research Integrity and Governance London School of Hygiene & Tropical Medicine, Keppel Street London, WC1E 7HT, UK Email: patricia.henley@lshtm.ac.uk Phone: +44 20 7927 2626</p>
Trial Management Group	<p>Danielle Beaumont, Senior Trial Manager, LSHTM Asia Kiyani, Pakistan Trial Coordinator Kiran Javaid, Pakistan Assistant Trial Coordinator Adetayo Olusade, Nigeria Assistant Trial Coordinator Olujide Okunade, Nigeria Assistant Trial Coordinator Danielle Prowse, Data manager, LSHTM Amy Brenner, Epidemiologist and Statistics, LSHTM Ian Roberts, Co-Chief Investigator, LSHTM Haleema Shakur-Still, Co-Chief Investigator, LSHTM</p>
Clinical Trials Unit (Global Coordinating Centre)	<p>Faculty of Epidemiology London School of Hygiene & Tropical Medicine, Keppel Street London, WC1E 7HT, UK Email: crash19@lshtm.ac.uk Phone: 020 7299 4684 Fax: 020 7299 4663</p>
Pakistan Coordinating Centre	<p>Global Institute of Human Development, Shifa Tameer-e-Millat University, Rawalpindi, Pakistan Email: pakistan.crash19@lshtm-ctu.org</p>
Nigeria Coordinating Centre	<p>University College Hospital, Ibadan Nigeria Email: nigeria.crash19@lshtm-ctu.org</p>

Appendix 6: Protocol change log

Version	Date	Description of Change	Brief Rationale
0.9 Draft	15/April/2020	First version submitted to LSHTM Ethics Committee	Not applicable
1.0	23/April/2020	Addition of Appendix 7; update dissemination plan, update definition of 'suspect case of COVID-19	LSHTM Ethics Committee recommendation

Appendix 7: Guidance on professional legal representatives

INFORMATION ON ACTING AS A PERSONAL OR PROFESSIONAL LEGAL REPRESENTATIVE

What is a legal representative?

In the context of clinical trials, specific legislations apply to protect the rights of people who are not able to make decisions for themselves. This includes safeguards for the conduct of research involving people who may, temporarily or permanently, not be able to consent due to a medical problem, for example because of severe illness, unconsciousness, learning disabilities, head injuries or mental health problems. In particular, clinical trial regulations require that before a person who is unable to consent is involved in a trial, another suitable person must be identified who can give consent for their enrolment in the trial, as their legal representative. You have been given this information because you have been identified as suitable to act as a legal representative by the research team. This sheet and the following participant information sheet will explain what this research will involve for you and the patient.

Why have I been approached?

A legal representative may be someone who has a personal relationship with the patient but does not have a conflict of interest, such as being part of the research project or gaining financial benefit. Examples of suitable people who might act in this manner are:

- A family member, carer or friend
- A court appointed deputy who has a personal relationship with the participant

When reasonable steps have been taken to identify a personal legal representative and one is unavailable, then the researcher must nominate a person to act on the patient's behalf. This person may be involved in the patient's care in a professional capacity but they must have no connection with the research project. A suitable person who might act as the professional legal representative is an independent doctor working with the patient or a person nominated by the healthcare provider.

What are the duties of a Legal Representative?

The main responsibility of the legal representative is to give their consent for the patient to be included in this research. The consent is optional, and if you do not provide this your decision will be respected.

In order to help you make the decision about acting as the legal representative, and to help you in deciding whether to give consent, the separate participant information sheet describes what is involved in the trial. This information is the same that given to patients who are able to make this decision for themselves.

What will happen if I agree?

If you agree for your friend / relative / patient to take part in the trial then they will be a full participant. The information sheet, which will be explained to you by a researcher, describes what this will involve. If you agree now you can withdraw your consent at any point in the future. If your friend / relative / patient regains capacity later, they will be asked whether they would like to continue taking part in the trial.