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.