**C-19-ACS**

# Preventing Cardiac Complication of COVID-19 Disease with Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial.

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**Sponsor**

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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**Funder**

Imperial College COVID Research Fund

**Disclaimer**

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This protocol describes the C-19-ACS study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.
Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| OR | Odds Ratio |
| ICU | Intensive Care Unit |
| COVID-19 | Novel Coronarvirus 2 related disease |
| SARS-CoV2 | Novel Coronavirus 2 |
| ACS | Acute Coronary Syndrome |
| NIHR | National Institute for Health Research |
| BD | Twice a day |
| OD | Once a day |
| LV | Left Ventricular |
| LMWH | Low Molecular Weight Heparin |
| DOAC | Direct Oral Anticoagulants |
| HES | Hospital Episode Statistics |
| BARC | Bleeding Academic Research Consortium |
| IHD | Ischemic Heart Disease |
| HIC | Health Informatics Collaborative |

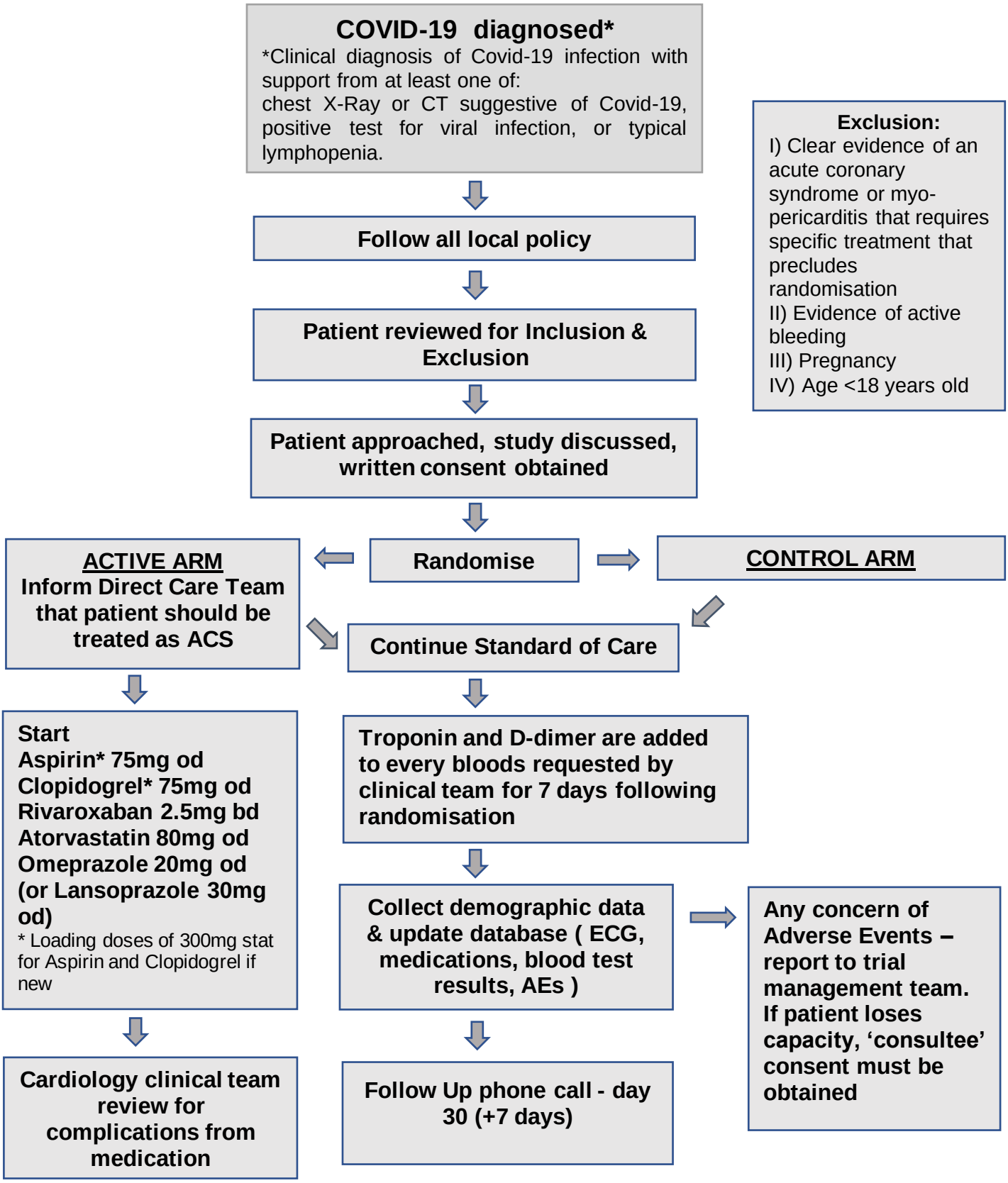
## KEYWORDS

Coronavirus, SARS-CoV-2, COVID-19, Cardiovascular, Outcomes.

## STUDY SUMMARY

| | |
|---|---|
| **TITLE** | Preventing Cardiac Complication of COVID-19 Disease with Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial. |
| **DESIGN** | Prospective Multicentre Randomised Controlled Trial |
| **AIMS** | To determine if undiagnosed acute coronary syndrome is a major cause of mortality in COVID-19. |
| **OUTCOME MEASURES** | **Primary:**<br>All-cause mortality at 30 days post randomisation.<br>**Secondary:**<br>1. peak troponin within 7- and 30-days post randomization<br>2. peak d-dimer within 7- and 30-days post randomization<br>3. time to discharge from hospital (length of stay) from randomization and from admission<br>4. need for non-invasive ventilatory support<br>5. need for invasive ventilatory support<br>6. need for inotropes or vasopressors<br>7. need for mechanical circulatory support (e.g. ECMO, Impella, IABP)<br>8. need for renal replacement therapy |
| **POPULATION** | Hospital inpatients |
| **ELIGIBILITY** | Clinical diagnosis of Covid-19 infection |
| **DURATION OF PATIENT INVOLVEMENT** | 30 days |
| **DURATION OF STUDY** | 1 year |

# C-19-ACS


COVID-19 diagnosed*
*Clinical diagnosis of Covid-19 infection with support from at least one of:
chest X-Ray or CT suggestive of Covid-19, positive test for viral infection, or typical lymphopenia.
Exclusion:
I) Clear evidence of an acute coronary syndrome or myo-pericarditis that requires specific treatment that precludes randomisation
II) Evidence of active bleeding
III) Pregnancy
IV) Age <18 years old
Follow all local policy
Patient reviewed for Inclusion & Exclusion
Patient approached, study discussed, written consent obtained
Randomise
ACTIVE ARM
Inform Direct Care Team that patient should be treated as ACS
CONTROL ARM
Continue Standard of Care
Start
Aspirin* 75mg od
Clopidogrel* 75mg od
Rivaroxaban 2.5mg bd
Atorvastatin 80mg od
Omeprazole 20mg od
(or Lansoprazole 30mg od)
* Loading doses of 300mg stat for Aspirin and Clopidogrel if new
Troponin and D-dimer are added to every bloods requested by clinical team for 7 days following randomisation
Collect demographic data & update database ( ECG, medications, blood test results, AEs )
Any concern of Adverse Events – report to trial management team. If patient loses capacity, 'consultee' consent must be obtained
Cardiology clinical team review for complications from medication
Follow Up phone call - day 30 (+7 days)

# 1. INTRODUCTION

## 1.1 BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the biggest public health challenge of the last century. There are two key observations from initial reports of patients requiring hospitalisation[1] which indicate that whilst supportive treatment of the primary respiratory problem is being delivered, preventing cardiac complications may be key to survival.

First, a history coronary artery disease appears to significantly increase the risk of mortality in SARS-CoV-2 with and odds ratio (OR) of 21.4 (95%CI 4.64–98.76). Even risk factors such as hypertension and diabetes increase mortality by OR 3.05 and OR 2.85 respectively[1]. These findings were echoed in another report of patients with COVID-19 requiring hospitalisation. Hypertension (58.3% vs 21.6%, p < 0.001) and cardiovascular disease (25.0% vs 10.8% p 0.04) were significantly more common in patients who required intensive care admission, compared to those that did not[2].

Second, damage to the heart appears to identify patients who are likely to die: troponin was elevated in around half (23/50) in those dying but was almost never raised (1/95) in those surviving[1]. Again, these findings are reproducible in the second large report of hospitalised patients with COVID-19. Acute cardiac injury (7.2% vs. 22% p <0.001) and arrhythmia (16.7 vs. 44.4% p < 0.001) were more common in patients who required intensive care[2]. Troponin elevations were noted in between 6 – 12% of all patients, and were significantly more common in patients requiring intensive care in both studies[1,2].

A recent meta-analysis of studies reporting cardiovascular outcomes of patients admitted to hospital with COVID-19 disease, including 6 studies and 1527 patients, identified a 17.1% rate of pre-existing cardiovascular disease in the entire cohort. The incidence of cardiovascular was threefold higher in patients who required intensive care. Furthermore, 8% of the entire cohort suffered an acute cardiac injury, an event thirteen times more likely in those requiring intensive care[3].

It is assumed that the myocardial damage in SARS-Cov-2 represents a form of myocarditis. There is currently no published histological data to show evidence of this. However, the association between myocardial infarction and influenza virus is well recognised[4]. The epidemiology of previously known viral myocarditis and SARS-CoV-2 is entirely different, with peak age of 20-40[4] (compared to the median age of 56 in SARS-CoV-2). In myocarditis there is no association between the presence of coronary disease and outcome[5]. The picture in myocarditis cohorts is of low prevalence of CAD risk factors with 11% hypertension, 4% hyperlipidaemia and 4% diabetes[6]. The patients dying in SARS-CoV-2 are very different – older, with confirmed or likely coronary disease, and we believe they may be suffering acute coronary syndromes in the setting of acute illness.

Another, potential link between SARS-CoV-2 and the cardiovascular system appears to be the angiotensin converting enzyme – 2 receptor (ACE2). ACE2 is abundant in myocardial cells and converts angiotensin II to angiotensin 1-7. This conversion appears to attenuate the pressor, proliferative and fibrotic effects of angiotensin II. SARS-CoV-2 appears to utilise the ACE2 receptor and result in a loss of function[7,8].

Regardless, it is normally possible to identify whether a troponin rise is due to acute coronary syndrome or myocarditis using cardiac MRI or biopsy. However, communication from colleagues in Italy indicates that these tests have proven impossible on the grounds of workload, patient instability and risks to healthcare workers. Because we cannot get this information, we cannot dissect out the mechanism of myocardial damage, and in this unusual situation we propose to proceed directly to a trial of widely available therapies used in acute coronary syndromes (ACS) across the UK, given the association between SARS-CoV-2 mortality and coronary disease and its risk factors. In order to effectively prevent the cardiac complication, we believe treatment should start before cardiac injury becomes apparent.

### 1.2 RATIONALE FOR CURRENT STUDY

This study is based on the observations that cardiovascular disease is a risk factor for severe forms of COVID-19 disease, and that acute cardiac injury is a predictor of poor outcome.

Currently, we believe that physicians do not prescribe the appropriate cardioprotective medications in these patients, despite evidence of myocardial injury due to the challenges posed in treating the illness caused COVID-19 disease. Most physicians are assuming that the cardiac injury in COVID-19 disease is driven by myocarditis and therefore have used drugs such as steroids to control it, but disappointingly without benefit. It can be very difficult to differentiate myocarditis from acute coronary syndromes in the context of the critical illnesses such as COVID-19. Investigations such as cardiac MRI and angiography may not be performed owing to the status of the patient.

Our hypothesis is that acute coronary syndromes are being left untreated in these patients and leads to the cardiac complications accountable for the majority of the mortality in COVID-19 disease.

To address this hypothesis it is going to be unrealistic to perform the diagnostic tests required, based on the experience of physicians in China and Italy. However, we could empirically treat these patients for acute coronary syndrome to determine if this is the primary cause of deterioration.

By randomising patients to receive ACS treatment and standard care, or standard care alone, we can establish the efficacy of therapy, and make advances in understanding the role of the cardiovascular system in COVID-19 disease.

## 2. STUDY OBJECTIVES

To determine if undiagnosed acute coronary syndrome is a major cause of mortality in COVID-19.

## 3. STUDY DESIGN

The study will be conducted in two phases, Phase I is powered to detect changes in biomarkers associated with myocardial injury. Phase I will be conducted at a limited number of hospitals. At an interim analysis of Phase I results, we will determine if there is evidence for justifying progress to Phase II, which is powered to detect changes in clinical outcome. In view of the urgency of the public health situation. We will set up Phase II whilst awaiting the results of Phase I. We will aim to have 30 hospitals set up so that if the interim analysis indicates benefit, REC approval will be sought to extend to Phase II multi-site study.

**Screening**
Physicians admitting patients with suspected COVID-19 infection will give the Patient Information Sheet to the patient and obtain written consent following admission. At Imperial College Healthcare, these patients will have an entry on the electronic patient record to allow identification by the research team. Potentially eligible patients medical record is screened by a member of the research team. This process will in include support from the National Health Informatics Collaborative. If inclusion criteria are met, and no exclusion criteria are present, the patient will

receive a PIS. If patients agrees they will be randomised. Any women of child-bearing age will need a negative pregnancy test prior to enrolment in to the study. Written consent will be obtained before any therapy is started. Patients will receive therapy as per their randomisation.

**Randomisation:**

This proposed study is a Randomised Controlled Trial. Randomisation will be in a 1:1 fashion using by a computer-generated randomisation list. Cross-over will not be permitted.

**Study Arms:**
**1. ACS Treatment (Trial Arm) and Standard Care**

Patients randomised to ACS therapy will be prescribed the following medications by a member of the cardiology team, or direct care team:

- If patient not on aspirin, add aspirin 75mg (after loading dose of 300mg stat) once daily unless contraindicated.
- If patient not on clopidogrel or equivalent, add clopidogrel 75mg (after loading dose of 300mg stat) once daily unless contraindicated
- If patient not on an anticoagulation, add rivaroxaban 2.5mg bd unless contraindicated
- If patient not on a statin, add atorvastatin 80mg once daily unless contraindicated
- If patient not on a proton pump inhibitor, add omeprazole 20mg or lansoprazole 30mg once daily.

Patients under certain scenarios have the following modified approach:

**(A)** Patient on DOAC on admission:
i) Start aspirin, clopidogrel, atorvastatin and omeprazole as per protocol
ii) Change DOAC to rivaroxaban 15mg OD (not rivaroxaban 2.5mg bd).
iii) At 28 days, stop all study medications and restart original routine medications.

**(B)** Patient on warfarin on admission for an indication which is also licensed indication for rivaroxaban
i) Start aspirin, clopidogrel, atorvastatin and omeprazole as per protocol
ii) Stop warfarin
iii) Start rivaroxaban 15mg OD when INR <3.0 (instead of rivaroxaban 2.5mg BD)
iv) At 28 days, stop all study meds and restart original routine meds.
v) Clinical team/Patient decision about whether to continue treatment dose rivaroxaban or restart warfarin after study.

**(C)** Patient on warfarin on admission for an indication which is not licensed indication for rivaroxaban (eg metallic valve, LV thrombus etc):
i) Give all drugs as per protocol except for Rivaroxaban & Aspirin.
ii) Remain on warfarin throughout (instead of Rivaroxaban 2.5mg BD)
iii) Stop other study drugs at 28days

**(D)** Atorvastatin should be reduced 20mg if Erythromycin or Clarithromcyin is used

**(E)** If patient is on Lansoprazole, then no need to switch to omeprazole

**(F)** There have been varying views about anticoagulation in COVID and standard of care is not clear. We would like to limit contamination with anticoagulants in the control arm as far possible and the following guidance is given;

(i) Prophylactic anticoagulation with LMWH is allowed in control arm.

(ii) If a thromboembolic event occurs then patient should be anticoagulated as per international guidelines for the condition. If they are in the intervention arm, then stop aspirin and continue clopidogrel
(iii) If there is a local clinical policy for therapeutic anticoagulation on the basis of elevated D-Dimer, this can be followed as per the local policy for the control arm. If this is to be applied to a patient in the intervention arm, then increase Rivaroxaban 2.5mg to Rivaroxaban 15mg OD in accordance with the protocol for patients already on therapeutic anti-coagulation for other indications.

**(G)** Recruitment to other studies and the compassionate use of drugs is allowed except where it involves the use of antiplatelets, anticoagulants or drugs being used for a cardiac pathology to avoid contamination

**(H)** If a patient develops an acute coronary syndrome needing coronary angiography and angioplasty;
Active Arm : Stop rivaroxaban and continue dual antiplatelets. Restart rivaroxaban after PCI according ESC guidelines.
Control arm: receives drug management according to local PCI standard of care.

**(I)** If patient is fed by NG tube: Use Aspirin oro-dispersible formulation, Clopidogrel & Atorvastatin crushed and mixed with water, Rivaroxaban crushed and mixed with water.Change Omeprazole to oro-dispersible lansoprazole 30mg

**(J)** If the patient is already taking a study drug or equivalent. If a patient is in the control arm and on any of the 'study' drugs or equivalent, these should be continued. If the patient is in the intervention arm, convert to study drugs and doses unless there is a clinical reason that this cannot happen eg allergy, side effects, previously tried and abandoned.

The justification for these drugs is based on previous studies and these are summarised below:

**Aspirin:** ISIS-2 (STEMI) - 23% reduction in vascular mortality in patients presenting with acute MI (AMI) ($p < 0.00001$), a benefit maintained alongside thrombolysis with streptokinase.

**Clopidogrel:** COMMIT (STEMI) - Significant reduction in death, reinfarction, or stroke (RRR 9%; p=0.002), Significant reduction in death (RRR 7%; p=0.03) CURE (NSTEMI) - Medical or invasive patients. The composite of CV death, MI and stroke was reduced versus aspirin alone (RR: 0.80; 95% CI: 0.72–0.90; $p < 0.001$). This was driven by a reduction in MI (RR: 0.77; 95% CI: 0.67–0.89) and cardiovascular mortality was similar between groups (RR: 0.93; 95% CI: 0.79–1.08)

**Rivaroxaban:** PIONEER AF – Combined anti-platelets and DOACs safely with patients randomised to 1:1:1 of 1) 15mg rivaroxaban & single antiplatelet OD, 2) 2.5mg BD rivaroxaban & aspirin OR clopidogrel, or 3) warfarin & dual anti-platelet therapy. ATLAS-ACS-2-TIMI-51 - Low dose rivaroxaban post MI added to DAPT in people who didn't have an indication for anti-coagulation reduced risk of composite of death from CV causes, myocardial infarction, or stroke, but increase bleeding.

**Atorvastatin** - PROVE-IT - atorvastatin 80mg od immediately following ACS reduces composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalisation, revascularization vs. pravastatin, benefit seen as early as 30 days.

**Omeprazole** - COGENT - Reduced bleeding with omeprazole with dual antiplatelet therapy with no obvious harm.

The aim is to continue study medications for 28 days, as there is a risk of delayed ischaemic events following viral illness.

Where the patient is already established on one, or a combination, of these medications the existing medications will be continued, and the remaining medications prescribed only.

If the patient has a contraindication an individual, or combination of, study medication this is not administered.

Daily blood tests would usually be standard of care for patients hospitalised with severe chest infections. Please confirm this is being practised with the direct care team and add troponin and D-dimer to these blood request if not being performed routinely. There is good evidence that these are markers of outcome. Please input the values from randomisation to day 7 (or day of discharge if this is earlier than day 7)

Standard care of the admitting team will not be altered by the research team.

**2. Standard Care (Control Arm)**

Standard care is at the discretion of the admitting team and will not be interfered with by the research team. Daily blood tests would usually be standard of care for patients hospitalised with severe chest infections. Please confirm this is being practised with the direct care team and add troponin and D-dimer to these blood request if not being performed routinely. There is good evidence that these are markers of outcome. Please input the values from randomisation to day 7 (or day of discharge if this is earlier than day 7)

**Measuring Endpoint Data and Follow Up:**

Scheduled clinical data checks will occur at enrolment, discharge from Hospital, and at 30 days. Unscheduled checks will be made if the research team is informed of an adverse event, there is other cause for concern, or if interim data is required for analysis. Clinical records may also be reviewed after the 30 day trial inclusion period to confirm data. This will cease at the study end.

A member of the research team will access the patient's medical record to do so.

If the patient's admission is less than 30 days (the duration of patient's follow up), follow up after discharge will occur on day 30 by telephone contact, or patients can make unscheduled contact with the research team. Telephone calls will be made only after reviewing clinical records HES data to ascertain if the patient is already deceased.
Study medications will be included in discharge medications to cover a total of 28 days should the patient be discharged before the 30 days.

The day 30 phone call will ideally be made on day 30, but may occur within a week of this date to prevent loss of this key data check point in case of surmountable variables such as patient not being available on the phone on a particular day.

The proposed follow up and endpoint assessments eliminate any need for researcher interactions with infected individuals minimising risk to researchers and to contacts of researchers, which may include other patients or vulnerable individuals in the community. This also reduces the burden of research activity demanded of recruited subjects who will have no mandatory research follow up visits.

**Study Duration:**

The total study duration for each participant will be 30 days. Overall study duration will be 1 year.

**Study Subjects:**

**Phase I:** Based on our power calculation to detect significant changes in biomarkers associated with myocardial injury, we aim to randomise 170 patients.

**Phase II:** Should Phase I show a significant benefit for the trial arm, we will proceed to Phase II of the study, where, based on our power calculation we aim to randomise 3000 patients to detect changes in clinical outcomes.

## 3.1 STUDY OUTCOME MEASURES

**Primary Efficacy Outcome**
1. All-cause mortality at 30 days post randomization

**Secondary Efficacy Outcomes**

1. peak troponin within 7- and 30-days post randomization
2. peak d-dimer within 7- and 30-days post randomization
3. time to discharge from hospital (length of stay) from randomization and from admission
4. need for non-invasive ventilatory support
5. need for invasive ventilatory support
6. need for inotropes or vasopressors
7. need for mechanical circulatory support (e.g. ECMO, Impella, IABP).
8. need for renal replacement therapy

**Primary Safety Outcomes (Phase I and II)**

1. Bleeding Academic Research Consortium (BARC) bleed event at 30-days post randomization.
2. BARC bleed level 5 (mortality) bleed event at 30-days post randomisation
3. thromboembolic event
4. adherence to the randomised arm
5. cessation of randomized active arm therapy
6. cessation of randomized active arm therapy due to safety concern or adverse event

Emerging safety outcomes monitored through:

1. Recorded adverse events and serious adverse events

## 3.2. METHODS OF ANALYSIS

The methods of statistical analysis will be laid out in a Statistical Analysis Plan, signed by the chief investigator, Trial Steering Committee chair, Senior statistician, and Trial Statistician. The method of analysis is briefly summarized below, but the language of the Statistical Analysis Plan will be governing.

**Principals**

All the analysis will be conducted on an intention-to-treat basis unless otherwise specified. Only participants withdrawing from data collection will be excluded from the analysis. All hypothesis tests will be two-sided. No correction for multiple testing for secondary outcomes will be made but all secondary outcomes will be reported for transparency of the number of tests undertaking. All analyses will be adjusted for randomization minimisation variables and other names variables used in the primary analysis (pre-specified in the SAP) unless otherwise stated.

**Primary analysis**

The primary outcome is all-cause mortality at 30-days post randomization. We will test the hypothesis that there is no difference in the odds of the primary outcome between the control and intervention groups using a mixed logistic regression model. The model will include the factors used for minimization and/or stratification (age, presence of diabetes, presence of coronary artery disease, and sex as fixed effects; and site as a random effect) and the following additional factors: (baseline log troponin level, hypertension, and known heart failure). Both unadjusted and adjusted Odds Ratios (OR) and their 95% Confidence Interval (CI) will be presented but the adjusted results will considered primary (Table 1: Adjusted results).

Observed mortality rate at 30-days post randomization will be tabulated for each arm (Table 1) with Kaplan-Meier survival curves presented.

A Bayesian analysis will also be undertaken using uninformative prior distributions using a logistic regression model. This analysis will be undertaken to provide an alternative interpretation of the treatment effect in terms of the posterior probability of the treatment strategy being superior to standard treatment.

Furthermore, a complier average causal effect (CACE) analysis will also be performed to estimate the effect of the treatment strategy when adhered to as planned in the protocol for the active arm.

Secondary efficacy analysis: Peak-troponin

7- and 30-day peak troponin will be compared between arm by using a linear regression model, including the log transformed baseline troponin including the same baseline variables as the primary model.

## 4. PARTICIPANT ENTRY

### 4.1 PRE-REGISTRATION EVALUATIONS

No specific pre-registration evaluations are required. All study assessments are made post-randomization.

### 4.2 INCLUSION CRITERIA

1. Clinical diagnosis of Covid -19 infection with support from at least one of the following: chest X-Ray or CT suggestive of Covid-19, positive test for viral infection, or typical lymphopenia.
2. Age =/>40 or diabetes or known coronary disease or hypertension
3. Requires hospital admission for further clinical management.

### 4.3 EXCLUSION CRITERIA

1. Clear evidence of an acute coronary syndrome or myo-pericarditis that requires specific treatment that precludes randomisation.
2. Evidence of active bleeding
3. Pregnancy.
4. Age <18 years

## 5. ADVERSE EVENTS

### 5.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical study subject.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### 5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

#### 5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

#### 5.3.2 Serious AEs

An SAE form should be completed and e-mailed to the trial mailbox and Chief Investigator within 24 hours. However, relapse and death due to COVID-19 and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the West London & GTAC Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

**Contact details for reporting SAEs**
**Trial Email: imperial.covidcardio@nhs.net**
**Imperial JRCO Email: jrco@imperial.ac.uk**
**Study CI Email: p.kanagaratnam@imperial.ac.uk**

## 6. ASSESSMENT AND FOLLOW-UP

If the patient's admission is less than 30 days in total, follow up after discharge will occur on day 30 by telephone contact, or patients can make unscheduled contact with the research team. We will check HES mortality data to ensure that patient is alive before we call them. This is primarily to confirm survival and any delayed bleeding complications.

The end of the study participation for patient occurs at day 30 after randomisation.

## 7. STATISTICS AND DATA ANALYSIS

### Sample Size Calculations

***Power Calculations for establishing if Troponin elevation can be prevented:***
Assuming a log-normal distribution, then applying the Wuhan[1] paper's distribution of an interquartile range of median/4 to median x 4, this is roughly an SD of log10(4)=0.6. So, if we assume we hope to lower the troponin by 2-fold, which is 0.3 log units, then to have 90% power to detect this at the 5% significance level, we will need to randomize 170 patients.

***Power Calculations for establishing if there is a mortality benefit***
Assuming a 25% mortality in the control arm based on the Wuhan retrospective data of COVID-19 positive patients being treated in hospital, then to have 90% power to detect at the 5% significance level, a drop in mortality to an absolute level of 20% (i.e. a Hazard ratio of 0.8), we would need to randomize 3000 patients.

## 8. REGULATORY ISSUES

### 8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the West London & GTAC Research Ethics Committee(REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 8.2 CONSENT

First, the pressure exerted by COVID-19 on healthcare services is projected to be the most significant for a generation. It is likely, owing to the rapid spread and lack of immunity to SARS-CoV-2, that this pressure will arrive simultaneously and reach peak extremely soon after. Therefore, healthcare providers assessing and managing these patients will have to divert all their attention to the clinical care of COVID-19 patients. Thus, the time required of healthcare providers involved in the direct care of COVID-19 patients, to obtain informed consent will be limited.

Secondly, an alternative approach to obtain informed consent would be to this via members of the research team. However, the risk of contracting SARS-CoV-2 for research members not involved in the direct clinical care of these patients is unacceptably high and could promote spread.

Therefore, patient will be approached only after screening and confirmation of eligibility has been done by the research team. Patient will be provided with patient information sheet and a telephone number to discuss any queries with study team. Written consent will be obtained prior to any study activities.

A large proportion of patients with COVID-19 would be unable to provide informed consent. The most common cause for this is delirium caused by infection and low oxygen levels. It is scientifically important to include this group of patients in our randomised controlled study. Therefore, we undertook a patient-public-involvement survey. Results of this survey show that there is strong support from the public that we include these patients.
In order to identify, where possible, patient's preferences regarding who will be acting as a personal consultee if patient will lose capacity while taking part in the trial, there is a section in the Patient Consent Form asking to provide the name and contact details of personal consultee if the need for one will arise.

If patient eligible to take part in the study is already lacking capacity to give consent, reasonable steps will be taken to identify 'personal consultee' from patient's clinical records and/or recommendations of direct care team (according to Section 32 of Mental Capacity Act 2005). If no appropriate person can be identified who is willing to act as a personal consultee, the researcher may consult a "nominated consultee", i.e. a person independent of the project appointed in accordance with the Department of Health's guidance on nominating a consultee for research involving adults who lack capacity to consent.

The consultee will be given information about the project and asked to advise on what the participant's wishes and feelings would be about taking part. The advice of the consultee will be respected. If the consultee so advises, the participant must not take part and, if already taking part, must be withdrawn unless withdrawal of treatment would involve significant risk to the participant's health.
If a 'nominated consultee' is appointed and completes the declaration form and an appropriate 'personal consultee' is subsequently identified, the 'personal consultee's' advice will override that of the 'nominated consultee'. If the 'personal consultee' advises that the participant would not wish to be in the research, the participant must be withdrawn from the study.
When participant will regain capacity, he/she will be approached by the member of local research team to discuss the study and obtain patient consent to continue participation. If participant indicates he/she wishes to be withdrawn, this will be done without delay unless there would be a significant risk to his/her health (Section 33 Mental Capacity Act 2005)..

We will gain consent from a personal consultee (next of kin/friend) until the patient becomes lucid and is able confirm consent is ongoing (be re-consented). The consent from next of kin will be by phone, e-mail and postal to endeavour to have written consent in place.

### 8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

### 8.4 INDEMNITY

Imperial College London holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study.

### 8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

### 8.6 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

## 9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the trial management group. There will be Steering, Safety and Endpoint committees appointed to oversee the study. Furthermore, a data monitoring committee will adjudicate the trial safety on a weekly basis.

## 10. PUBLICATION POLICY

Trial results will be released in several manuscripts providing outcomes of the trial as a whole. All publications and presentations relating to the trial will be authorised by the Trial Steering Committee. Named authors will include the Investigators from all participating investigational centres.

## 11. REFERENCES

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**APPENDIX 1.**

**Summary of investigations, treatment and assessments**

| **Assessment** | | **Week of Treatment** | | | |
|---|---|---|---|---|---|
| | **Admission to hospital with confirmed COVID-19** | 1 | 2 | 3 | 4 |
| Patient identified | X | | | | |
| PIS provided to patient | X | | | | |
| Written Consent obtained | X | | | | |
| Confirmation that cardiac biomarkers are added to routine clinical blood draws, whilst inpatient. | X | X | X | X | X |
| Clinical diagnosis of Covid-19 infection with support from at least one of the following; chest X-Ray or CT suggestive of Covid-19, positive test for viral infection, or typical lymphopenia. | X | | | | |
| 30 day follow up phone call | | | | | X |

**APPENDIX 2:**

**Imperial College Healthcare NHS Trust Workflow**

| Work flow | Person responsible | Comments |
|---|---|---|
| Cases that meet inclusion criteria can be extracted from Cerner:<br>Diagnosis of Covid 19<br>More than 40yrs<br>Below 40ys with any of Diabetes Mellitus, hypertension or history of IHD | HIC Team* | Ideally we want to identify patients within 24 hours of admission so that ACS therapy has the best opportunity to be effective but will be dependent on time for test results to come back<br><br>HIC team can screen patients having COVID tests as well so some screening can be done prior to final result |
| Review of cases for eligibility<br><br>Exclusions:<br>Clear evidence of an acute coronary syndrome or myo-pericarditis that requires specific treatment that precludes randomisation.<br>Evidence of active bleeding<br>Pregnancy.<br>Age <18 years | Research Nurse | May need to manually review cases for inclusion/ exclusion criteria depending on extraction capability. |
| Eligibility verified by Doctor | Research Fellow or Clinical SpR | |
| PIS given to Ward Team | Research Nurse | |
| PIS given to patient | Ward Team/ Research Nurse/Research Practitioner | |
| Patient consented | Research Fellow/Research Nurse/Research Practitioner/ Clinical SpR | |
| Eligible patients randomised | Research Nurse | Electronic randomisation with age and sex matching |
| Clinical team check and prescribe ACS therapy | Clinical team looking after patient | Prescribe ACS medication according to BNF contraindications. Request troponin and D-dimer blood tests to be added to all routine blood tests for at least 7 days following randomisation – for study participants in both arms. |
| Check patient has had medication prescription | Research Nurse | Check 24 hours later |

| | | |
|---|---|---|
| Data reviewed for input into database at enrolment, discharge, day 30 and as necessary (eg for review of adverse events, data analysis) | HIC team*, Research Nurse, Research Fellow | All data required for database can be pulled from Cerner. |
| Safety monitoring | Research fellow | Safety monitoring committee will review any adverse events in case study needs to be stopped early. |
| If patient discharged before 30 days | Research Nurse | Ensure patient discharged on ACS medication for 28 days<br>Phone call at 30 days to assess end points and ensure all new drugs have been stopped and study letter sent to GP. |

***HIC Team:**
The NIHR Health Informatics Collaborative (HIC) was initially made up of five BRCs and their respective NHS Trusts and university partners – Oxford University Hospitals NHS Foundation Trust, Imperial College Healthcare NHS Trust, Guy's and St Thomas' NHS Foundation Trust/Kings College Hospital NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust and University College London Hospitals NHS Foundation Trust. Since then the collaborative has expanded to include 23 NHS Trusts from across England.

The aim of the HIC is to improve the availability and quality of routinely captured hospital data and to make it available for multi-site translational research. The collaborative then uses this data in an anonymised form to answer pressing clinical and research questions, helping us understand the complex care delivered in the NHS and how care can be improved to provide the best services to patients.

Collecting data directly from electronic patient record systems drastically reduces the time and cost for data collection for research, and allows for the creation of much larger datasets compared to traditional research projects, which rely on recruiting patients individually.

The use of routinely captured data does however also bring its own challenges. The fact that each participating NHS site has its own electronic patient record system means that data are captured differently at each trust; this can make the process of compiling all sites' data into one dataset challenging. Additionally, not all data are collected electronically at each site, and large amounts of crucial electronic data are often recorded in free text rather than in a structured format.
The HIC overcomes these issues by creating data warehouses at each site that read in and transform data to standardised structures and formats, validating and cataloguing data so that it is clear what the data was captured for and how it should be used. The collaborative also has projects running that aim to extract structured data from free text and share methods and codes across the NHS to reduce duplication of methods.