Statistical Analysis Plan (SAP)

Preventing Cardiac Complications of COVID-19 Disease with Early Acute Coronary Syndrome Therapy trial

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SAP V2.0

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1 Approval Signatures

Name	Signature	Role	Date
		Chief Investigator	
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2 Contents

3 Abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse event
BRC	Biomedical Research Centre
C-19-ACS	Preventing Cardiac Complications of COVID-19 Disease with Early Acute Coronary Syndrome Therapy
COVID-19	Novel Coronavirus 2 Related disease
DMC	Data Monitoring Committee
DOAC	Direct Oral Anti-Coagulant
SARS-CoV2	Novel Coronavirus 2
CI	Confidence Interval
CRF	Case Report Form
HIC	Health Informatics Collaborative
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICTU	Imperial Clinical Trials Unit
ICU	Intensive Care Unit
NIHR	National Institute of Health Research
PO	Per Os (oral route)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

4 Introduction

This statistical analysis plan (SAP), which is based on protocol Version 5.0 dated 12 October 2020 defines the methods and analyses that Imperial College London plans to use to analyze the data from the Preventing Cardiac Complications of COVID-19 Disease with Early Acute Coronary Syndrome Therapy trial (henceforth, C-19-ACS). This study adheres to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928), and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It is being conducted in compliance with the protocol, the Data Protection Act, and other regulatory requirements as appropriate. If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

5 Study objectives

This study is based on observations during the COVID-19 pandemic that

· cardiovascular disease, such as hypertension, diabetes, and previous myocardial infarction are disproportionately associated with poorer outcomes.

· significant acute cardiac injury is occurring in patients with COVID-19 and is similarly associated with poor outcomes

The mechanism of this cardiac damage is not clear. One possibility is that, due to the coagulopathy associated with COVID-19, this represent an acute coronary syndrome (ACS).

We will therefore test this hypothesis by randomizing patients to standard ACS therapies (Aspirin, Clopidogrel, Rivaroxaban, Atorvastatin, and Omeprazole) to see if they have an impact on cardiovascular outcomes.

5.1 Primary objective:

The main objective of this study is to:

- determine if an ACS-like pathophysiology underlies cardiovascular complications in COVID-19

The primary efficacy outcome is:

- all-cause mortality at 30-days post randomization.

5.2 Secondary objectives

The secondary objectives are to monitor surrogate markers of efficacy and safety.

The key secondary outcome will be:

- an ordinal outcomes scale (ranging from 1 - dead to 4 – at home)

This outcome was added to the Statistical Analysis Protocol as an amendment (Version 2). The addition of an ordinal outcome scale to the secondary endpoint was made without reference to unblinded data from this trial. This change was based on recommendations from

- Emerging statistical practices of other randomised controlled trials in COVID.
- Public recommendations from various health authorities (WHO) and biostatisticians involved in COVID research.

The motivation to utilise it as the key secondary outcome arose after the DSMB reviewed the data completeness of the blinded troponin and d-dimer data. A significant proportion of patients were discharged home within 1 or 2 days of randomisation. The meant that serial, in-hospital blood results were not able to be obtained and the original planned analysis is untenable.

The secondary efficacy outcomes include:

- mortality at 90 days (pending protocol change)
- peak troponin within 7- and 30-days post randomization
- peak d-dimer within 7- and 30-days post randomization
- time to discharge from hospital (length of stay) from randomisation and from admission
- need for non-invasive ventilatory support
- need for invasive ventilatory support
- need for inotropes or vasopressors
- need for mechanical circulatory support (e.g. ECMO, Impella, IABP).
- need for renal replacement therapy

The secondary pre-specified safety outcomes include:

- Bleeding Academic Research Consortium (BARC) bleed event at 30-days post randomization.
- BARC bleed level 5 (mortality) bleed event at 30-days post randomisation
- thromboembolic event

- adherence to the randomised arm
- cessation of randomized active arm therapy
- cessation of randomized active arm therapy due to safety concern or adverse event

Emerging safety outcomes monitored through:

- Recorded adverse events and serious adverse events

5.3 Primary objective of internal pilot (Phase 1)

In order to ensure the study is a worthwhile undertaking and is safe we have included an internal pilot to assess the potential for bleeding harms.

The SAP was amended (version 2) to remove the assessment of efficacy from the objectives at the interim analysis. This change was made based on a blinded assessment of data completeness by the trial steering committee after recommendations were made by the data monitoring committee. Similarly, the effect on troponin and d-dimer were from the objectives of the interim analysis.

- To evaluate the harm profile of the combined treatment with a focus on bleeding outcomes.
- To assess the recruitment process and data collection quality.
- To check the control event rate included in the sample size calculation for Phase 2.
- To monitor adherence to the randomised arm (assessing the potential for contamination)

Internal pilot outcomes:

- Bleeding Academic Research Consortium (BARC) bleed at 30-days post randomization
- recruitment rate
- proportion of missing data for key outcomes
- control event rates

6 Design

6.1 Study design

Parallel two arm randomized, single blind controlled trial with internal pilot.

C-19-ACS is a study determine if Acute Coronary Syndrome (ACS) is a major cause of mortality in patients with Novel Coronavirus 2 Related Disease (COVID-19) in patients. The study will randomize patients with confirmed COVID-19 in hospital to a 28-day course of standard ACS treatment to determine if the established ACS therapy has an impact on cardiovascular-outcomes.

The trial will include two phases: phase 1 and phase 2. Phase 1 will act as an integrated internal pilot with a close evaluation of safety, assessment of recruitment, contamination and quality of data collection. In phase 1, recruitment will include a minimum 170 patients of the total 3062

needed for the trial. The phase 1 analysis will occur after approximately 170 participants have 7 days follow-up information available. The result will be reviewed by an independent Data Monitoring Committee (DMC) who will make a recommendation to continue or halt the trial based on safety, or feasibility/quality issues. The DMC will also monitor the mortality event rate throughout the trial with the potential to recommend an increase to the sample size if it is assessed that increasing the precision of the treatment effect estimate will likely help inform subsequent policy treatment decisions through strengthening of evidence.

If there are no concerns at the end of phase I assessment, the trial will continue onto phase 2 in which a further approximately 30 sites will be recruited.

6.2 Treatment groups

Patients will be randomized 1:1 ratio to the intervention group or control.

The intervention group will receive a combination of standard, evidence-based, therapies typically used for treatment of ACS. These are:

- If not already on Aspirin, Aspirin 75mg once daily PO (without a loading dose), unless contra-indicated
- If not already on clopidogrel or an equivalent anti-platelet agent, Clopidogrel 75mg once daily PO (without a loading dose), unless contra-indicated
- If not already on anti-coagulation, Rivaroxaban 2.5mg twice daily PO, unless contra-indicated.
- If not already on a statin, Atorvastatin 40mg once daily (evening) PO, unless contra-indicated
- If patient not already on a proton-pump inhibitor or equivalent, Omeprazole 20mg once daily PO, unless contra-indicated.

Previous or active use of any of the treatment medications will not be an exclusion to enrolment and randomization. Should, in the treating physician's option, there be any contra-indication to any single component of the ACS therapy, this single component will not be given, but other components will continue.

Should a patient in the arm randomized to the control group already be taking a component of the ACS therapy, this will be continued.

6.2.1 Treatment group management under specific situations

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 (e.g. mechanical heart valve, LV thrombus):

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) Patient receiving Erythromycin or Clarithromcyin during the study period.

i) Atorvastatin should be reduced 20mg

(E) Patient receiving Lansoprazole

i) Continue lansoprazole, do not start Omeprazole

(F) There is no clear consensus with regards to the standard of care prophylactic anticoagulation in patients with COVID. 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 the 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:

i) Intervention Arm: Stop Rivaroxaban and continue dual antiplatelets. Restart Rivaroxaban after PCI according ESC guidelines.

ii) Control arm: Receive drug management according to local PCI standard of care.

(I) If patient is fed by NG tube:

i) Use Aspirin oro-dispersible formulation,

ii) Clopidogrel & Atorvastatin crushed and mixed with water

iii) Rivaroxaban crushed and mixed with water.

iv) 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 e.g. allergy, side effects, previously tried and abandoned.

6.2.2 Duration of study medications

The study medications will be continued for 28 days with the patients provided with the remaining medications at discharge from hospital.

6.2.3 Alternate medications

This study will not alter any of the medication of patients randomized to the control group. Patients will continue to receive their existing medication and any therapies their clinical team consider appropriate.

6.3 Study population

This study will recruit patients admitted to hospital with symptomatic, laboratory confirmed, acute SARS-CoV2 infection (confirmed COVID-19) with risk factors for complications. The current method of laboratory confirmation is based on RT-PCR (RdRP gene assay) from nasal swabs, but alternate molecular methods of confirmation may be used as they become available.

6.4 Eligibility criteria

6.4.1 Inclusion criteria

Patients must meet all the following inclusion criteria.

- 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.
- Age =/>40 or diabetes or known coronary disease or hypertension
- Requires hospital admission for further clinical management.

6.4.2 Exclusion criteria

Patients who meet any of the below exclusion criteria will not be recruited.

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

6.5 Blinding

The patient, clinical team, and trial recruitment team are not blinded to the therapy.

Members of the trial team will regularly screen the patient's inpatient notes and EHR for adverse events. Upon detecting an adverse event an outcome adjudication will be completed, with trial arm redacted. These will be submitted to the blinded end-point adjudicated committee.

Assessment of the outcomes collected at 30-days by telephone will be performed by a member of the trial team who at the beginning of the call will blinded to the trial arm. After obtaining information on mortality, re-admissions, and other end-point the member of the trial team will then unblind themselves so they can instruct the patient about cessation of trial medications.

6.6 Sample size

Estimating the required sample size for the trial is challenging as a good estimate for the mortality rate with standard treatment strategies for ACS in the UK will not be known for a while. There are further challenges with shifting clinical practice and the government recommendations will could alter the 'at risk' population and standard treatment given. As a result we have chosen to size the trial in the first instance based on the best available data we have and use recognised parameters within this calculation (90% power and 5% significance level) (6.6.1). However, given the great uncertainties and potential shifts we do not aim to restrict this trial to a narrow hypothesis-testing framework. The aim of this study is to estimate the effect of the treatment strategy effect with good precision. The power calculation included in 6.6.1 will ensure we have a good prospect of this. This means interpretation will not be restrict using a single binary threshold of 5% significance, but the p-value will be interpreted on the continuous scale as strength against the null hypothesis. This will be presentation of the treatment effect estimate and 95% confidence intervals. The DMC will monitor the assumed all-cause mortality rate and will advise on extending the trial if they deem greater precision will result in better information for decision-making.

A Bayesian analysis will also be undertaken on the primary outcome to further encourage intelligent interpretation of study results. This will allow us to report on the posterior probability for 30-day all-cause mortality being superior in the ACS treatment strategy arm compared to standard treatment approach. In addition, a Bayesian analysis of the longitudinal ordinal outcomes over the 30 day follow-up period.

6.6.1 30-day all-cause mortality

Assuming 25% mortality in the control arm (Wuhan retrospective data of COVID-19 patients requiring in-hospital treatment), 3000 patients will provide 90% power at the 5% significant level to detect a 20% reduction in mortality. Inflating the number to account for missing outcome data in 2%, we plan to recruit and randomize 3062 participants.

6.7 Schedule of time and events

6.7.1 Scheduled visits

Potential participants (patients within the inclusion criteria presenting with likely or confirmed COVID-19 infection) will be screened by the research team after review by their clinical medical team. Patients will be approached by the research team, the study discussed, and the patient given a participant information sheet (PIS).

Once COVID-19 infection is confirmed, eligible patients will be consented and enrolled by a member of the study team and then randomized using the in-house randomization mobile phone application "1minclusion".

The study team will make a note in the patient's electronic health record (EHR) about the trial, the patient's enrolment, and the randomization arm. For patients randomized to the active arm, the study team will make a request to the clinical team to prescribe the study medications barring any contra-indications to individual medication. This will be confirmed by a review of the EHR by the study team.

Whilst the patient remains in-hospital, follow-up is via electronic patient health records. The study team will ensure that the study blood tests (such as troponin) are added to routine clinical blood samples.

After discharge, patients will receive phone calls at day 30 and day 90 (pending protocol change) by a member of the study team blinded to the randomization arm.

If contact is lost, their GP will be contacted by a member of the study team blinded to the randomization arm to obtain the 30 and 90-day outcomes.

	Recruitment	**In-hospital stay (unblinded study team)**	**Follow-up (blinded study team)**	
	Day 0	Every day	Day 30	Day 90 (pending protocol change)
PIS provided to patient	X			
Patient recruited with written consent	X			
Ensure study blood biomarkers are added to routine clinical blood draws	X	X		
Ensure blood biomarkers and outcomes are entered in the eCRF			X	X
Confirmation of SARS-CoV-2 test positivity	X			
Follow-up telephone call			X	X

6.7.2 Unscheduled visits

Unscheduled assessments are not performed unless participants develop adverse events that the chief investigator considers 'related' to the trial medications.

6.8 Randomization

Participants will be allocated using minimization in a 1:1 allocation ratio using the in-house "1minclusion" recruitment and randomization mobile application. The minimization algorithm will operate over the variables:

- Age > 60
- Presence of diabetes (of any type)
- Presence of coronary artery disease

- Sex

and will be stratified by recruitment site.

7 Populations of analysis sets

7.1 Intent-to-treat / randomization population

The intent-to-treat population will include all randomized participants in the arms there were allocated to regardless of subsequent treatment received. The analysis will be conducted on an intention-to-treat basis and will include all participants in the arm they were allocated to and for which we have outcome data.

7.2 Safety population

The primary safety population will be the intention-to-treat population as the primary objective of the trial is to estimate the efficacy and safety of the treatment strategy. Additional analysis taking into account exposure will be undertaken where there are emerging events of interest and for pre-specified bleeding outcomes.

7.3 Per protocol population

It is likely that a proportion of control patients will receive some elements of the treatment group's medications. Therefore, the difference of the two arms will be reduced and the primary ITT results may become biased in the direction of no difference. To address this possible issue compliance to all drug treatments will be monitored in both arms. This will include the starting dates if the study treatments and the number of days when each study medication was taken during the follow up.

A complier average causal effect (CACE) analysis will be performed to estimate the effect size, in those that received the treatment strategy as planned.

8 Variables of analysis

8.1 Baseline and demographic variables

The following baseline variables will be captured with measures of centrality and distribution reported:

- Age
  - Age > 60
- Sex
- Ethnicity
- Past medical history
  - Hypertension
  - Diabetes
  - Known coronary artery disease
- Medication use
  - Aspirin
  - Clopidogrel.
  - Other anti-platelet agents.
  - Oral anticoagulant
  - Direct oral anticoagulant usage
  - Usage of prophylactic dose low-molecular weight heparin
  - Usage of treatment dose low-molecular weight heparin
  - Statin
  - Proton pump inhibitors
- Biomarkers
  - Haemoglobin
  - C-reactive Protein (CRP)
  - D-dimer
  - Troponin
- Hospital admission
  - Time from symptoms to admission
  - Time from admission to randomization
- Site

8.2 Primary efficacy variable

30-day all-cause mortality post randomization collected by from in-hospital records or telephone follow up.

8.3 Secondary efficacy variables

The key secondary efficacy variable is:

- An ordinal outcome measure (ranging from 1- death to 4 – discharged home)

Other secondary efficacy variables are:

- all-cause mortality at 90-day post randomization collected from in-hospital records and telephone follow up (pending protocol change).
- peak troponin within 7- and 30-days post randomization collected from in-hospital records and data from the NIHR BRC HIC.
- time to discharge from hospital (length of stay) collected from in-hospital records
- need for non-invasive ventilatory support collected from in-hospital records
- need for invasive ventilatory support collected from in-hospital records
- need for mechanical circulatory support collected from in-hospital records
- need for renal replacement therapy collected from in-hospital record

Safety variables

- Bleeding Academic Research Consortium (BARC) bleed event at 30-days post randomization collected from in-hospital records and telephone follow up.
- cessation of randomized active arm therapy from in-hospital records and telephone follow up.
- cessation of randomized active arm therapy due to safety concern from in-hospital records and telephone follow up.

8.4 COVID ordinal outcome scale

The ordinal outcome scale is based on the FDA Centre for Drug Evaluation 7-level COVID ordinal outcomes scale, with modifications related to our ability to discriminate between the different levels.

- ***Level 1*** (dead) was kept unchanged.
- Level 2 (hospitalized, on ECMO or invasive mechanical ventilation) and level 3 (hospitalized, on high flow O2 therapy or non-invasive mechanical ventilation) were merged to form a new ***Level 2 (in hospital, advanced level care)***. This was done as throughout the pandemic differing emphasis was placed on the safety and availability of high-flow, non-invasive, and invasive mechanical ventilation. These therapies collectively represent requiring a higher level of care.
- Level 4 (hospitalized, on supplemental O2) and Level 5 (hospitalized, not on supplemental O_2 were merged to form a new Level 3 ***(in hospital, standard level care).*** This was done for two reasons. Whilst patient u, capturing the

- Level 6 (not hospitalized, unable to resume normal daily activities) and 7 (not hospitalized, able to resume normal daily activities) were merged to form ***Level 4*** (at home). This was done as the 30-day phone call was not protocolled to collect the patient's current level of physical activity.

The relationship between the ordinal scale used in this trial are shown in Table 1

Reference description	C-19-ACS Level
1 Dead	***1 Dead***
2 Hospitalized, on ECMO or invasive mechanical ventilation	***2 In hospital, advanced level care***
3 Hospitalized, on high flow O2 therapy or non-invasive mechanical ventilation	
4 Hospitalized, on supplemental O2	***3 In hospital, standard level care***
5 Hospitalized, not on supplemental O2	
6 Not hospitalized, unable to resume normal daily activities	***4 At home***
7 Not hospitalized, able to resume normal daily activities	

Table 1: Ordinal scale used for the key secondary endpoint. Relationship between the original levels and descriptions and those used within this trial

9 Statistical methodology

9.1 General methodology

Descriptive and inferential statistics will be used to summarize results of the C-19-ACS study. Continuous variables will be summarized using the number of subjects (N), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Discrete variables will be summarized using counts and percentages.

Summaries will be provided for demographics, medical history, concomitant medications, and adverse events. For summaries of medical history, concomitant medications, and AEs, the Medical Dictionary for Regulatory Activities (MedDRA®) and the World Health Organization Drug dictionaries, as appropriate, will be used.

9.2 Analysis principles

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.

9.3 Missing data principles

9.3.1 Missing outcome data

The primary analysis will include all participants with known all-cause mortality outcome at 30 days. Significant missingness in mortality data is not expected as outcome data can be obtained from registries. The primary outcome variable will not be imputed in the main analysis.

9.3.2 Missing baseline data

We anticipate that missing baseline data will be minimal and attempts to collect missing baseline data will be made at the follow-up visits. Unknow factors of the medical history will be considered and entered to the CRF as "No". For missing baseline variables planned to be included in the main analysis models, if there are a reasonable proportion of participants with at least one missing value in order to avoid losing the participants from the models, values will be imputed using the mean value calculated from the non-missing values pooled data from both treatment arms. For categorical variables use of an indicator variable will be used [White 2005]

9.3.3 Missing troponin detection limits

It is possible that the lower detection limit will be missing for some of the troponin measurements. If the measurement is below the lower detection limit but the limit is missing for the given measurement, then it will be imputed in the following way:

- If the patient had a measurement before with an available lower detection limit, then we will impute the limit with last observation carried forward method assuming that the new measurement has most likely the same limit.
- Similarly, if the lower detection limit is missing and there aren't any limits from before but there is after then the first following available limit will be imputed.
- If none of the patient's measurements has available detection limits, then the most frequent limit of that centre will be imputed.

9.4 Subgroups

The impact of pre-specified sub-groups treatment efficacy will be investigated by including an interaction terms for sub-group variables with treatment arm in the model. This will be in the secondary analysis.

The following sub-groups will be explored through tests of interaction tests in the relevant model with interpretation of the p-value in terms of strength against the null hypothesis and as hypothesis generating, rather than using a binary threshold as it is likely these analysis will be under-powered.

- Sex
- Age
- Ethnicity
- Baseline troponin
- Baseline d-dimer

9.5 Patient flow (CONSORT diagram)

The patient flow (CONSORT diagram) is included in the protocol, and will follow recommendations of Moher et al 2001.

9.6 Baseline demographics

Baseline demographics and variables will be summarized as described by the general methodology section.

9.7 Phase I interim analysis

Interim analysis will include descriptive statistics of all outcome variables listed in 5.3, by arm. The primary efficacy analysis (as in section 9.8), safety analysis as outlined in section 9.10.

9.8 Primary efficacy analysis - All-cause mortality at 30-days post randomization

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 (as outlined in Appendix A), hypertension, and known heart failure). Both unadjusted (**Error! Reference source not found.**) 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.

9.8.1 Supplementary analysis to the primary analysis 1

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.

9.8.2 Supplementary analysis to the primary analysis 2

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.

Compliance in the active arm will be defined at participants who received at least 50% of the planned dose (whilst alive) for the treatments they would have been eligible for at the time of randomisation. The complier average causal effect will be estimated by a two-stage least squares instrumental variable regression. Randomisation is taken to the instrumental variable for treatment received and there will be adjustment for the fixed effect variables used in the primary model. Analysis will be undertaken using the Stata using "ivregress 2sls" command or equivalent.

9.9 Secondary efficacy analysis

9.9.1 Bayesian analysis of the longitudinal ordinal outcome scale

This data will be analyses using the exemplar analysis plan for "Sequential parallel-group RCTs for COVID-19" published by the FDA center for Drug Evaluation and Research Office of Biostatistics, with the extension to longitudinal ordinal outcomes [http://hbiostat.org/proj/covid19/bayesplan.html], and using the worked example [https://hbiostat.org/proj/covid19/orchid.html]. In brief, a longitudinal ordinal model will be generated including age, sex, presence of diabetes, presence of coronary artery disease, and site. Priors and model decisions will follow the worked example as closely as possible.

The benefit of a longitudinal ordinal model is that as compared to a simple time–to-event analysis, full use of the available data is made. Simulations suggest the effective sample size can be increased by a factor of 5 with the addition of longitudinal data over 28 days [https://hbiostat.org/R/Hmisc/markov/].

9.9.2 90-day All-cause mortality (pending protocol change)

This will be calculated in a similar way to 30-day mortality.

9.9.3 Peak troponin and d-dimer within 7- and 30-days post randomization

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. The methods detailed in Appendix A will be used to incorporate the baseline troponin in the model.

9.9.4 Discharge form hospital (length of stay)

Discharge from hospital will be analysed using Cox proportional hazard models to test the hypothesis that there is no difference in this between the control and intervention groups. Kaplan-Meier survival curves, median length of hospital stay, and the log-rank test result will also be presented. Both adjusted (age, sex, baseline troponin level, hypertension, diabetes, heart failure) and unadjusted Hazard Ratios (HR) and their 95% Confidence Interval (CI) will be presented. The adjusted results taken as primary. For Cox regression models the proportionality assumption will be assessed graphically (using diagnostic plots). If the assumption does not meet the median difference and the result of log rank test will be presented.
Both the length of stay from admission and length of stay from randomisation will be presented.

9.9.5 Binary outcomes (need for invasive ventilatory support, mechanical circulatory support, renal replacement therapy, ECMO)

Binary outcomes including:

- need for non-invasive ventilatory support
- need for invasive ventilatory support
- need for mechanical circulatory support
- need for renal replacement therapy

will be compared between the arms using logistic regression adjusting for the stratification factors and for variables included in the primary model. The aim of this model is to test if there is a significant difference in these binary outcomes and to estimate the magnitude of the difference. Results will be presented as odds ratios compared to the control group and their 95% confidence intervals.

9.10 Safety analysis

9.10.1 Bleeding Academic Research Consortium (BARC) bleed event at 30 days

The BARC bleed event at 30-days will be analysis using a proportional odds model, including the same baseline variables as the primary model. The aim of this model is to test if there is a significant difference in these ordinal outcomes and to estimate the magnitude of the difference. Results will be presented as odds ratios compared to the control group and their 95% confidence intervals.

9.10.2 Bleeding Academic Research Consortium (BARC) grade 3 to 5 bleed event at 30 days

This will be calculated in a similar way to the primary outcome.

9.11 Interim analysis

The interim analysis will be performed after a minimum of 170 participants have been recruited and have a minimum of 7 days follow-up. The DMC will be responsible for reviewing all the data and advising on whether the trial should continue.

The following outcomes will be summarized by arm and compared between arm by calculating odds ratios, incidence rate ratios for count outcomes, or differences in mean. Safety summary statistics and between arm comparisons will be tabulated. Differences will be presented with 95% confidence intervals and p values, but the p-values will be interpreted in terms of strength of evidence using the continuous scale and not based on a binary threshold (e.g. 0.05).

- Bleeding Academic Research Consortium (BARC) bleed at 30-days post randomization
- peak troponin within 7- and 30-days post randomization
- recruitment rate
- proportion of missing data for troponin and mortality where due.
- Control event rates

A Kaplan Meier estimate for survival will also be presented with 95% CI around the curves

9.12 Subgroup analysis

The details of the planned subgroup analyses are presented in 9.4.

9.13 Tables to present

9.13.1 Adjusted logistic regression Model

Coefficients	Odd Ratio	[95% Conf. Interval]	
Treat			
Age			
Sex= F			
Log Troponin x 1000			
Etc			

Table 1: Adjusted results

9.13.2 Unadjusted Logistic regression model

Coefficients	Odds Ratio	[95% Conf. Interval]	
Treat			

Table 2: Unadjusted results

9.13.3 Observed percentage of events

Treatment	Days	N	Events	Cumulative event rate	95% CI Lower bound	95% CI Upper bound
Control	7					
Control	14					
Treatment	7					
Treatment	14					

Table 1

9.14 Figures to present

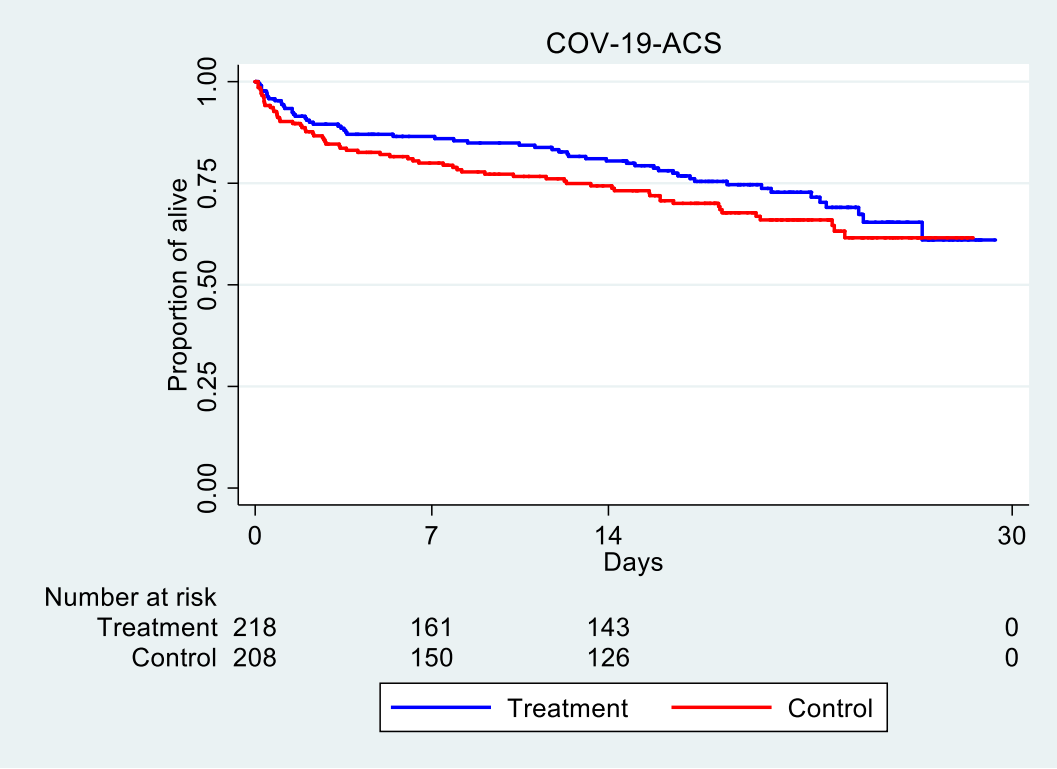

Figure 1

10 Amendments

10.1 Version 1.0

Nil

10.2 Version 2.0

1) Addition of an ordinal outcome scale as key secondary endpoint.
2) Addition of a longitudinal ordinal model as key secondary analysis.
3) Removal of d-dimer and troponin analysis from key interim analysis.

11 REFERENCES

White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Statistics in Medicine. 2005;24(7):993-1007.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. The Lancet. 2001;357(9263):1191-4.

12 Appendix A: Statistical methods for including troponin level and lower detection limit in the model

Troponin assumed to be a strong predictor of the primary outcome thus it might be associated with the other outcomes as well. Troponin levels, both baseline and peak levels will be log transformed and panned to be added to the models using restricted cubic splines using the methods described by Frank Harrell **[**https://discourse.datamethods.org/t/comparing-2-biomarkers-using-restricted-cubic-splines-how-to-interpretation-model-building/663/15**].**

We assume a proportion of the measurements will be below the lower detection level. Additionally, the lower detection level could be different between the tests used even for the same patients. To overcome this issue four variables will be used:

- Troponin level: log transformed added as restricted cubic splines (***troponin***)
- Detection indicator variable 1: binary, 1 if there is an available measurement, 0 if measurement was taken but it is below the lower detection level (***detected1***)
- Detection indicator variable 2: binary, 0 if there is an available measurement, 1 if measurement was taken but it is below the lower detection level (***detected2***)
- Lower detection level: the threshold level of the given test, categorical or continuous depending on the number of different levels (***detection_level***)

These will be added to the model in the following way for both logistic regression and Cox models:

$$Outcome_i = Treament_i + minimsation\ varaibles_i + \boldsymbol{detected_1} * \boldsymbol{rcs}(\mathbf{log}\ \boldsymbol{troponin}, \mathbf{3}) + \boldsymbol{detected_2} * \boldsymbol{detection\ level}$$

This method will be used for both baseline and peak troponin levels (if used) depending on the aim of modelling.

The first interaction term (***detected1 * detection_level***) as a non-zero value if there is a detected troponin and in this case the second interaction term is always zero.

The interaction term (***detected2 * detection_level***) has a non-zero value if troponin was below the detection level and in this case the first interaction term is always zero. This term will show the role of detection level if "not detected" associated with the outcome. The range of the coefficients of the different detection levels will show how sensitive is the outcome to the various detection levels.